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07/13/93

12C

PATENT APPLICATION
Docket No. SPC89-05-11227

GP1205 - 7.299

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Timothy J. Barberich and James W. Young

Serial No.: 07/896,725 Group Art Unit: 1205

Filed: June 9, 1992 Examiner: L. Schenkman

For: METHOD FOR TREATING ASTHMA USING OPTICALLY PURE R(-) ALBUTEROL

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service as First Class Mail in an envelope addressed to Honorable Commissioner of Patents and Trademarks, Washington, D.C. 20231 on July 14, 1993
HAMILTON, BROOK, SMITH & REYNOLDS, P.C.

B.J. Harris July 14, 1993
Signature Date

93 JUL 26 AM 10:18

ASSOCIATE POWER OF ATTORNEY

The Honorable Commissioner of Patents
and Trademarks
Washington, D.C. 20231

Sir:

The undersigned, as attorney of record, hereby grants to Philip E. Hansen, Registration No. 32,700, of the firm of Heslin & Rothenberg, 450 New Karner Road, P.O. Box 12695, Albany, New York 12212-2695, an Associate Power of Attorney in the above-captioned application.

Please continue to send all correspondence to the attention of the undersigned attorney at Hamilton, Brook, Smith & Reynolds, P.C., Two Militia Drive, Lexington, MA 02173.

Respectfully submitted,

Patricia Granahan

Patricia Granahan
Registration No. 32,227
Attorney for Applicant(s)
(617) 861-6240

Lexington, Massachusetts

Dated: July 13, 1993

PATENT APPLICATION
DOCKET NO. SPC89-05

Expedited Procedure Under 37 C.F.R. 1.116
Examining Group 1205

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

#20

Applicant(s): Timothy J. Barberich and James W. Young

Serial No.: 07/896,725 Group Art Unit: 1205

Filed: June 9, 1992 Examiner: L. Schenkman

For: METHOD FOR TREATING ASTHMA USING OPTICALLY PURE R(-) ALBUTEROL

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service as First Class Mail in an envelope addressed to Honorable Commissioner of Patents and Trademarks, Washington, D.C.20231, on

July 23, 1993

B.J. Klemis
Signature

July 23, 1993
Date

93 JUL 30 A11:10:28

The Honorable Commissioner
of Patents and Trademarks
Washington, D.C. 20231

Sir:

Transmitted herewith is a response in the above-identified application.

[X] Small entity status of this application under 37 C.F.R. 1.9 and 1.27 has been established by a verified statement previously submitted.

[ ] A verified statement to establish small entity status under 37 C.F.R. 1.9 and 1.27 is enclosed.

The fee has been calculated as shown below:

	(COL. 1) CLAIMS REMAINING AFTER AMENDMENT		(COL. 2) HIGHEST NO. PREVIOUSLY PAID FOR	(COL. 3) PRESENT EXTRA	SMALL ENTITY RATE	SMALL ENTITY ADDIT. FEE	OR	OTHER THAN SMALL ENTITY RATE	OTHER THAN SMALL ENTITY ADDIT. FEE
TOTAL	* 11	MINUS	** 21	0	X 11	$ 0		X 22	$
INDEP	* 3	MINUS	*** 3	0	X 37	$ 0		X 74	$
[ ] FIRST PRESENTATION OF MULTIPLE DEP. CLAIM					+115	$		+230	$
					TOTAL =	$ 0			$

DLEV012209

☐ Please charge my Deposit Account No. 08-0380 in the amount of $_____.

☐ A check in the amount of $_____ is attached.

☐ A separate Petition for Extension of Time is being filed concurrently herewith.

☐ Payment for the extension fee is included with the petition.

☐ Deposit Account No. 08-0380 is being charged for the extension fee.

☒ The Commissioner is hereby authorized to charge payment of the following fees associated with this communication or credit any overpayment to Deposit Account No. 08-0380.

☒ Any filing fees under 37 C.F.R. 1.16 for the presentation of extra claims.

☒ Any patent application processing fees under 37 C.F.R. 1.17.

Any extensions of time that are required to maintain this application in a pending status, if not included herewith, are hereby requested. The Commissioner is hereby authorized to charge such extension fees to Deposit Account No. 08-0380. Two copies of this transmittal letter are enclosed for accounting purposes.

Respectfully submitted,

HAMILTON, BROOK, SMITH & REYNOLDS, P.C.

By Richard W. Wagner
Richard W. Wagner
Registration No. 34,480
Agent for Applicant(s)
(617) 861-6240

Dated: July 23, 1993

A:\AMFEE.FO

SPC89057
RWE:18
7/22/93

MAIL ROOM
JUL 26 1993
43
PAT. & TMK. OFF.

PATENT APPLICATION
Docket No. SPC89-057
Expedited Procedure under 37 C.F.R. 1.116
Examining Group 1205

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner of Patents and Trademarks
BOX AF

Applicant: Timothy J. Barberich and James W. Young

Serial No.: 07/896,725 Group Art Unit: 1205

Filed: June 9, 1992 Examiner: L. Schenkman

Title: METHOD FOR TREATING ASTHMA USING OPTICALLY PURE R(-) ALBUTEROL

#28 I (WE) JLP 7/30/93

93 JUL 30 AM 10:28

CERTIFICATE OF MAILING

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HAMILTON, BROOK, SMITH & REYNOLDS, P.C.

B. J. Rosenthal July 23, 1993
Signature Date

Amendment After Final Action Under 37 CFR 1.116

The Honorable Commissioner
of Patents and Trademarks
Box AF
Washington, D.C. 20231

Sir:

This is in response to the official action of June 7, 1993 (Paper Number 26), which requires response by September 7, 1993.

Please amend the application as follows:

In the Claims:

Claim 18, line 2 change "R-albuterol" to -- R(-)albuterol--.

Remarks

Claims 1 to 6, 8, 9, 13 and 14 were presented in the application as filed. Claims 9, 13 and 14 were canceled and claims 15 through 18 added in applicants' response mailed to the

Patent Office on February 10, 1993. Claims 1 to 6, 8 and 15 to 18 are therefore presently pending in the application.

Claim 18 has been amended according to the suggestion of the examiner to correct a typographical error.

In the Office Action of June 7, the rejection of all of the pending claims under 35 U.S.C. §103 was reiterated and made final. In addition, the examiner indicated that the applicants' arguments of February 10 and the Aberg Declaration submitted therewith were not persuasive.

In the new discussion in paragraph 6 of the Office Action, the examiner states "Note the summary of the Brittain et al article regarding the desirability of using the R(-) isomer and its effects on β-adrenoreceptors." The Summary section in the Brittain reference does not address the "desirability" of using the R-isomer; it states that the R-isomer is more potent. Applicants have previously explained that potency does not equate with desirability; other factors must be considered. (E.g., Chloramphenicol is more potent than penicillin V, but in most cases it is not more desirable.)

Moreover, it is not understood by applicants why the teachings of Brittain are isolated and emphasized by the examiner when the equally valid teachings of Hartley and Middlemiss are available which show that the racemate is 1.5 times as potent as the R-isomer. The analysis of selected pieces of the art has been found improper by the CCPA in *In re Kuderna* (165 USPQ 575). The issue of patentability must be approached "in terms of what would have been obvious to one of ordinary skill in the art at the time the invention was made in view of the sum of all the relevant teachings in the art." [Emphasis in original] In the previous response, applicants have analyzed the teachings of the art taken as a whole; the substance of that response is summarized below.

The thrust of applicants' invention is the reduction of side effects, which arise in the treatment of asthma with racemic albuterol, by the administration of R-(-)-albuterol in place of

Patent Office on February 10, 1993. Claims 1 to 6, 8 and 15 to 18 are therefore presently pending in the application.

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In the new discussion in paragraph 6 of the Office Action, the examiner states "Note the summary of the Brittain et al article regarding the desirability of using the R(-) isomer and its effects on β-adrenoreceptors." The Summary section in the Brittain reference does not address the "desirability" of using the R-isomer; it states that the R-isomer is more potent. Applicants have previously explained that potency does not equate with desirability; other factors must be considered. (E.g., Chloramphenicol is more potent than penicillin V, but in most cases it is not more desirable.)

Moreover, it is not understood by applicants why the teachings of Brittain are isolated and emphasized by the examiner when the equally valid teachings of Hartley and Middlemiss are available which show that the racemate is 1.5 times as potent as the R-isomer. The analysis of selected pieces of the art has been found improper by the CCPA in *In re Kuderna* (165 USPQ 575). The issue of patentability must be approached "in terms of what would have been obvious to one of ordinary skill in the art at the time the invention was made in view of the sum of all the relevant teachings in the art." [Emphasis in original] In the previous response, applicants have analyzed the teachings of the art taken as a whole; the substance of that response is summarized below.

The thrust of applicants' invention is the reduction of side effects, which arise in the treatment of asthma with racemic albuterol, by the administration of R-(-)-albuterol in place of

racemic albuterol. Side effects of drugs which, like albuterol, have a predominant β_2 agonist component, can arise from a number of interactions, one of which is addressed by the cited prior art: interaction of the primarily β_2-agonist drug with β_1 receptors. The Brittain, Hartley, Hawkins and Buckner references address the comparative interaction of albuterol isomers with β_1 vs β_2 receptors. None of the references shows that there is any β-selectivity advantage of R over S or over racemic. On the contrary, Buckner concludes that the ratios of tracheal (β_2) to atrial (β_1) activities of R and S are indistinguishable. The earlier Aberg Declaration confirmed that the references by Brittain, Hartley, Hawkins and Buckner do not teach any expectation of decreased side effects from the administration of the pure R isomer as compared to the racemate.

Thus, at the time of filing of applicants' parent application (1/5/90), the references cited would not have motivated a person of ordinary skill to administer the pure R(-) isomer of albuterol for the treatment of asthma on the basis of its receptor selectivity.

The examiner has suggested that increased potency might be a basis for separating enantiomers. However, to the contrary, and mindful that applicants' disclosure does not relate to potency, the art does not encourage the artisan of ordinary skill to resolve and administer pure R albuterol on the basis of potency. The reason for this lack of encouragement is because the theoretical advantage of a pure enantiomer is at most two-fold. A racemate, being a 50:50 mixture, simply acts like half a dose of the pure enantiomer and half a dose of filler. Since chemical resolution of racemic mixtures is never 100% efficient, a resolution will always yield less than 50% of the single isomer. Thus, unless one enantiomer antagonizes the effect of the other, there is no potency-based reason to suffer the loss of material attendant upon their resolution.

A potency ratio significantly greater than 2 between a

single enantiomer and its racemate would be consistent with antagonism by one enantiomer and would provide motivation for resolving the racemate. No such teaching is found in any of the references. Therefore, at the time of filing, the art did not suggest using pure R(-) albuterol either for lessened side effects or for potency enhancement. This conclusion was supported by the earlier Declaration of Dr. Aberg.

The examiner has suggested that applicants show comparative therapeutic indices to support their contention of lessened side effects. Applicants provide herewith the Declaration of Dr. Gunnar Aberg to establish that the results of Chapman and of Morley, in view of additional studies now performed by applicants, would indicate to the person of skill in the art that the R-isomer would have a higher therapeutic index in humans than would the racemate. The tests are accepted in the art as being predictive of efficacy in treating humans, and the pending method of use claims are narrowly drawn to the specific use for which the tests are predictive. (See *Ex parte Chwang*, 231 USPQ 751). Thus, as a matter of law, an adequate showing has been made to support patentability of the pending claims.

The examiner has further cautioned the applicants that a showing, if made, might not be persuasive in light of *In re Adamson*. In *Adamson*, the CCPA held that in establishing that one isomer was more potent, the applicants had "done no more than is suggested by the prior art and have ascertained no more than what would be expected by one skilled in the art." [Emphasis added] In the present case, applicants have shown that the art, taken as a whole, does not suggest that the resolution of the racemate and the use of R-(-)-albuterol substantially free of its S-isomer would provide therapy for asthma while simultaneously reducing side effects. Thus, the demonstration of improved therapeutic index by applicants should be persuasive in light of *In re Adamson*.

For the above stated reasons, applicants believe that the rejections under 35 U.S.C. §103 have been overcome. Applicants

respectfully request reconsideration of the application and allowance thereof. If the examiner feels that a telephone conversation would expedite prosecution of this application, he is asked to call applicants' agent at (617) 861-6240.

Respectfully submitted,

Richard W. Wagner

Richard W. Wagner
Agent for Applicants
Registration No. 34,480
(617) 861-6240

Lexington, MA 02173

Dated: July 23, 1993

DECLARATION

The Honorable Commissioner
of Patents and Trademarks
Box AF
Washington, D.C. 20231

Dear Sir:

I, Gunnar Aberg, declare:

THAT I am a citizen of Sweden and a resident of the Town of Westborough, Worcester County, Massachusetts;

THAT I am Vice-President of Research and Development, Pharmaceutical Division, Sepracor, Inc., Marlborough, Massachusetts. From 1968 to 1973 I was Director of Pharmacology at Bofors-Nobel Pharma, from 1974 to 1978 I was Group Leader in General Pharmacology at AB Haessle, from 1978 to 1980, I was Director of Pharmacology at Astra Pharmaceuticals, from 1980 to 1982 I was Director of Cardiovascular Pharmacology at Ciba-Geigy;

and from 1982 to 1988 I was Director of Pharmacology, and from 1988 to 1992 Executive Director of Pharmacology, at Bristol-Myers Squibb;

THAT I am a graduate of the University of Linkoping, Sweden from which I hold a Ph.D. in Pharmacology and of the University of Goteborg, Sweden from which I hold a Ph.D. in Zoophysiology, and that I hold the title of Docent (Associate Professor) in Applied Pharmacology at the University of Linkoping, Sweden;

THAT I have twenty-five years' industrial experience in the area of research pharmacology;

THAT I am an author of 86 articles on pharmacology, including ten articles on adrenergic β-blockers and β-agonists and that I am an inventor on seven U.S. patents and six pending U.S. applications and that I have made numerous presentations before professional societies and in universities on the subject of adrenergic drugs;

THAT I have reviewed the Office Action dated June 7, 1993 in the above case. I have also reviewed the application in the above case and the publications of Morley et al. [Brit. J. Pharmacol. 104, Suppl. 295P (1991)] and Chapman et al. [Trends in Pharmacological Science 12 231-232 (1992)], and as a result of my review and general knowledge of the subject area, I make the following analysis:

In the instant application, Barberich and Young disclose an unexpected diminution in side effects when the pure R-isomer of albuterol is administered. The literature cited in the office action, which was published prior to applicants' filing date, provides no evidence for an advantage of either enantiomer of albuterol on the basis of β_1 vs β_2 specificity.

The above-identified recent publications of Morley et al. and Chapman et al. provide newly available support for applicants' disclosure. These references disclose that the S(+) isomer of albuterol in guinea pigs causes a hypersensitivity to allergen. The authors concluded from their experiments that the

desired bronchodilator effect was prone to tachyphylaxis while the undesirable hypersensitivity to spasmogens was less prone to tachyphylaxis. Indeed, in the Chapman et al. paper the authors recommend that it may be prudent to remove enantiomers that were previously thought to be biologically inert. Their results support a previously undisclosed advantage to the use of pure R-enantiomer in that the side effect of paradoxical hypersensitivity is likely to be ameliorated.

Since the studies by Morley and Chapman were all performed *in vivo*, studies have now been performed under my direct supervision to investigate the effects of the albuterol isomers on bronchial smooth muscle preparations *in vitro*. These experiments were performed to determine whether the mechanism by which S(+)albuterol increased airway resistance was a direct effect on bronchial smooth muscle or was due to some undefined mechanism that may be species-specific to guinea pigs.

In these experiments, isolated tracheal muscle preparations were repeatedly subjected to graded doses of spasmogens, such as carbacholine. (It has been shown in previous studies that the effects of betareceptor agonists on isolated bronchial smooth muscle preparations are similar in human and guinea pig preparations.) After the tissues had been caused to contract, with increasing concentrations of carbacholine (10^{-8}M to 10^{-4}M), they were washed and some tissues were incubated for 90 min. with RS-, R(-), or S(+) albuterol at a concentration of 10^{-6}M, while other tissues were control tissues, incubated with the Ringer solution only. After the incubation period, the tissues were again carefully washed and subjected to renewed contractions with the spasmogen.

Results are presented in Figs. 1 through 4. It was found that the contractile response to the spasmogen was significantly ($P < 0.01$) increased in bronchial tissue strips that had been incubated with S(+)albuterol. No such effect was seen in tissues that had been incubated with R(-)albuterol, while the sensitizing

effect of the racemate was masked by the presence of the bronchodilating effect of the R(-) isomer. One may therefore conclude that the increased sensitivity to spasmogens by S(+)albuterol is due to direct effects on bronchial smooth muscles, rather than to undefined and possibly species-specific mechanisms.

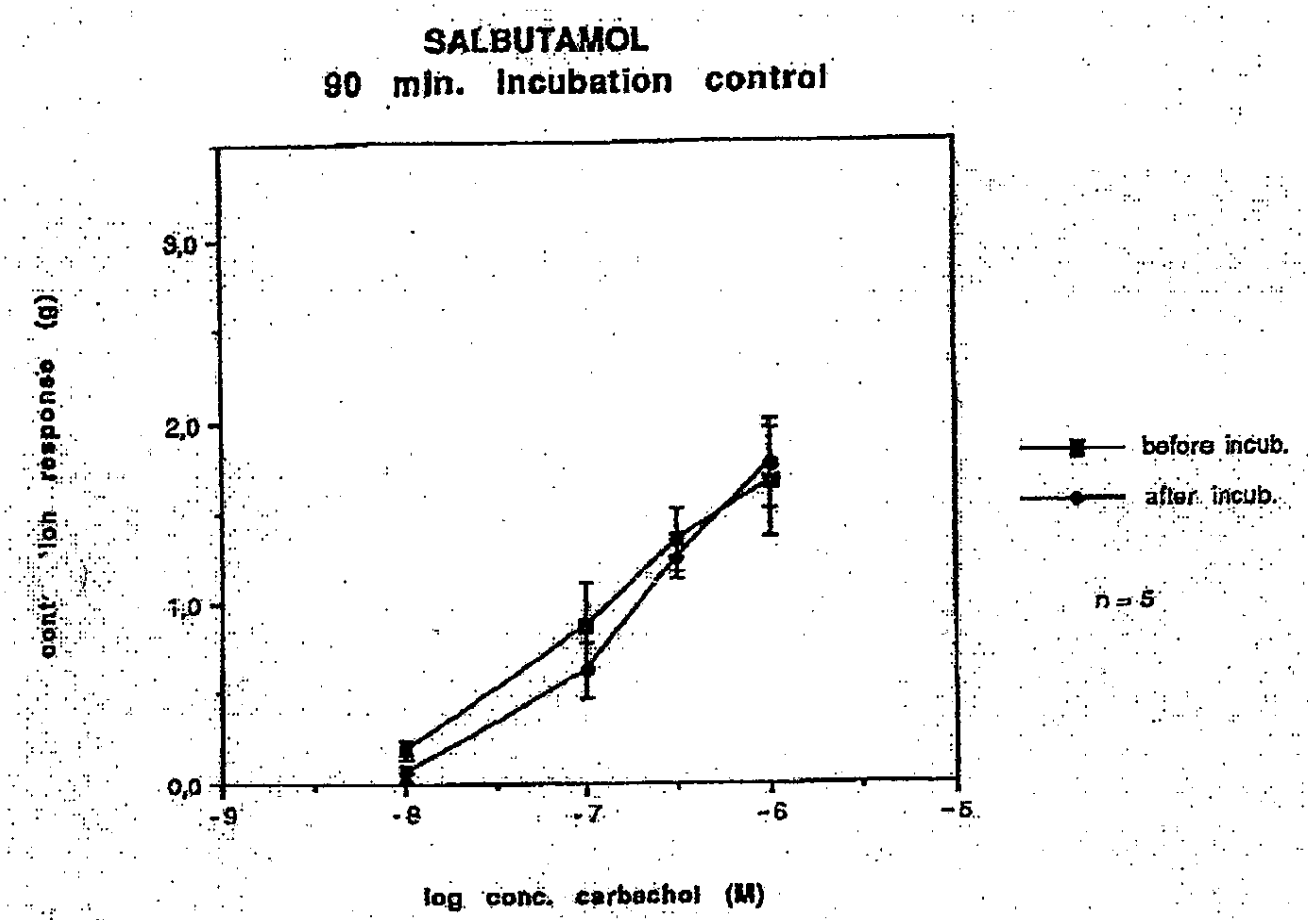

Fig. 1. Dose/response curves for carbacholine concentrations in isolated bronchial smooth muscle preparations. Control experiments.

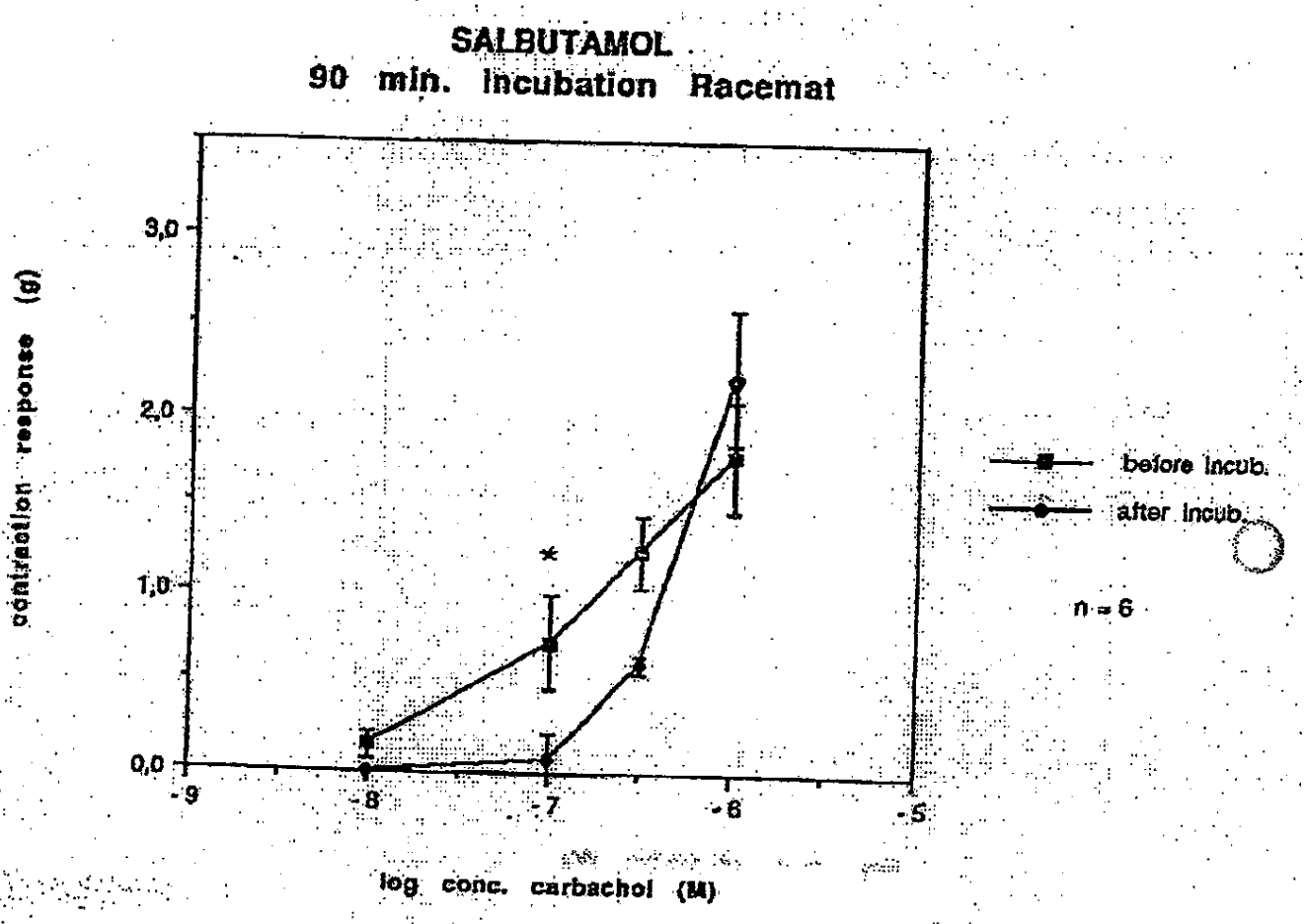

Fig. 2. Dose/response curves for carbacholine concentrations in isolated bronchial smooth muscle preparations before and after incubation with racemic albuterol (salbutamol).

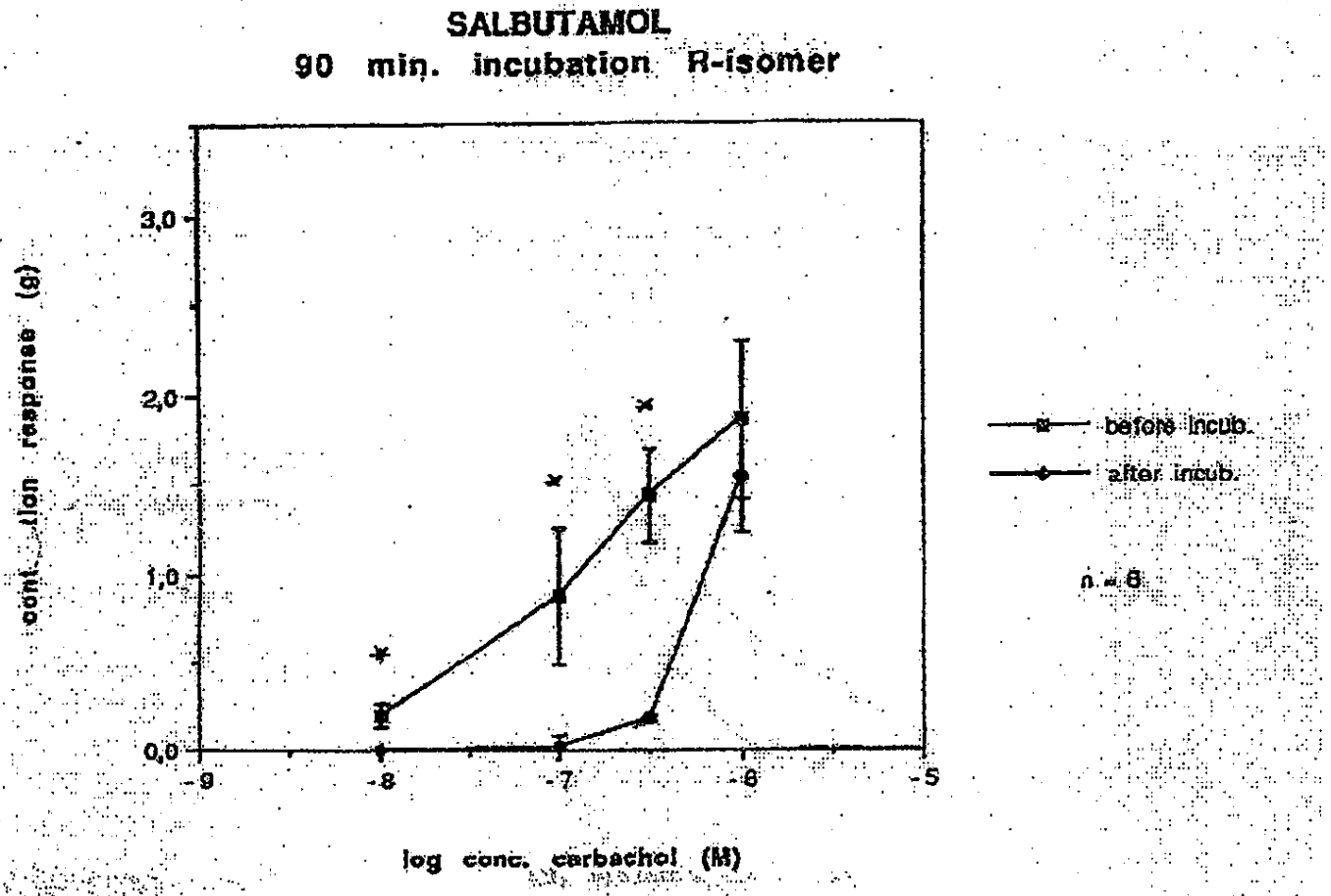

Fig. 3. Dose/response curves for carbacholine concentrations in isolated bronchial smooth muscle preparations before and after incubation with R(-)albuterol (salbutamol).

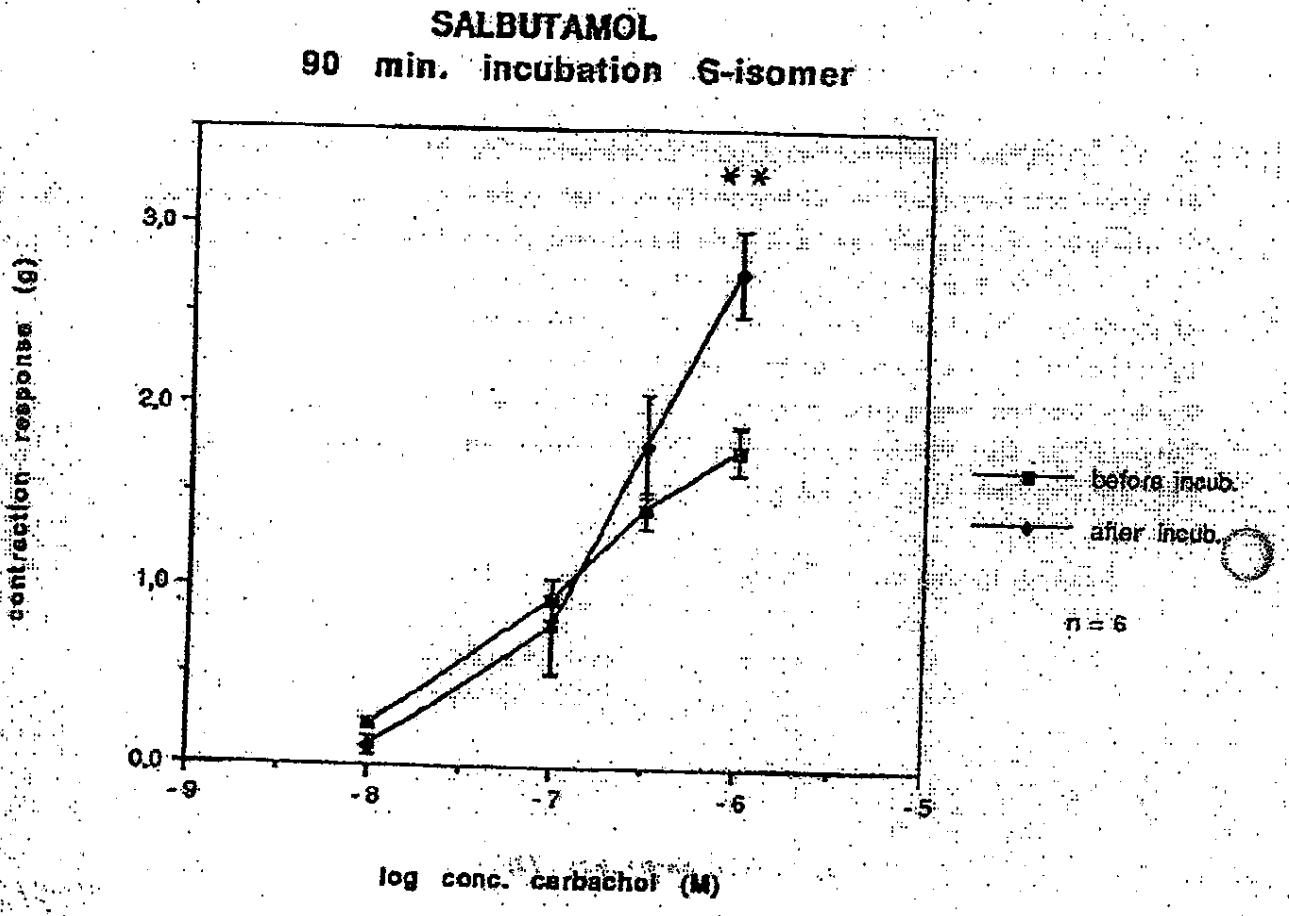

Fig. 4. Dose/response curves for carbacholine concentrations in isolated bronchial smooth muscle preparations before and after incubation with S(+)albuterol (salbutamol).

The experiments of Chapman et al. and Morley et al. in guinea pigs, in conjunction with our above-described studies, are tests which would be accepted by persons of skill in the brochodilator art as predictive of efficacy and of side effects in humans. They would indicate to the person of skill that R(-)albuterol will have a higher therapeutic index than racemic albuterol with respect to the side effect of hypersensitivity.

I further declare that all statements of the foregoing declaration made of my own knowledge are true and that those made upon information and belief are believed true and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that willful false statements may jeopardize the validity of the above-identified application or any patent issuing thereon.

Signed by me this 19th day of July 1993.

Gunnar Aberg

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

SERIAL NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
07/896,725	06/09/92	BARBARICH T	SPC89-

12M2/0803

PATRICIA GRANAHAN
HAMILTON, BROOK, SMITH & REYNOLDS
TWO MILITIA DRIVE
LEXINGTON, MA 02173

SCHENKMAN EXAMINER	
ART UNIT	PAPER NUMBER
1205	30

DATE MAILED: 08/03/93

Below is a communication from the EXAMINER in charge of this application

COMMISSIONER OF PATENTS AND TRADEMARKS

ADVISORY ACTION

☒ THE PERIOD FOR RESPONSE:

☐ is extended to run _____ from the date of the Final Rejection

☒ continues to run 3 mo. from the date of the Final Rejection

☐ expires three months from the date of the final rejection or as of the mailing date of this Advisory Action, whichever is later. In no event however, will the statutory period for response expire later than six months from the date of the final rejection.

Any extension of time must be obtained by filing a petition under 37 CFR 1.136(a), the proposed response and the appropriate fee. The date on which the response, the petition, and the fee have been filed is the date of the response and also the date for the purposes of determining the period of extension and the corresponding amount of the fee. Any extension fee pursuant to 37 CFR 1.17 will be calculated from the date that the shortened statutory period for response expires as set forth above.

☐ Appellant's Brief is due in accordance with 37 CFR 1.192(a).

☒ Applicant's response to the final rejection, filed 7/26/93 has been considered with the following effect, but it is not deemed to place the application in condition for allowance:

1. ☐ The proposed amendment(s) to the claim and/or specification will not be entered and the final rejection stands because:

   a. ☐ There is no convincing showing under 37 CFR 1.116(b) why the proposed amendment is necessary and was not earlier presented.

   b. ☐ They raise new issues that would require further consideration and/or search. (See Note).

   c. ☐ They raise the issue of new matter. (See Note).

   d. ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal.

   e. ☐ They present additional claims without cancelling a corresponding number of finally rejected claims.

   NOTE: _____

2. ☐ Newly proposed or amended claims _____ would be allowed if submitted in a separately filed amendment cancelling the non-allowable claims.

3. ☒ Upon the filing of an appeal, the proposed amendment ☒ will be ☐ will not be, entered and the status of the claims in this application would be as follows:

   Allowed claims: _____

   Claims objected to: _____

   Claims rejected: 1-6, 8 + 13-18

   However:

   a. ☐ The rejection of claims _____ on references is deemed to be overcome by applicant's response.

   b. ☐ The rejection of claims _____ on non-reference grounds only is deemed to be overcome by applicant's response.

4. ☒ The affidavit, exhibit or request for reconsideration has been considered but does not overcome the rejection.

5. ☐ The affidavit or exhibit will not be considered because applicant has not shown good and sufficient reasons why it was not earlier presented.

☐ The proposed drawing correction ☐ has ☐ has not been approved by the examiner.

☐ Other: The declaration is not persuasive since differences between the claimed invention and the prior art, whether regarding increased activity or altered pH effect, are not unobvious.

Leonard Schenkman
LEONARD SCHENKMAN
PRIMARY EXAMINER
GROUP 1200

PTOL-303 REV 3-90

DLEV012225

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> 444
       03aug93 17:15:56 User072820 Session D72.1
            $0.18    0.005 Hrs File1
     $0.18  Estimated cost File1
     $0.06  DIALNET
     $0.24  Estimated cost this search
     $0.24  Estimated total session cost    0.005 Hrs.

File 444:New England Journal of Med.  1985-1993/Jul W4
       (c) 1993 Mass. Med. Soc.
ALERTS can now be set up in file 444.

      Set  Items  Description
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?s py=1992 and au=spitzer, w?
            1315  PY=1992
               2  AU=SPITZER, W?
      S1       2  PY=1992 AND AU=SPITZER, W?
?t/3/all

 1/3/1
00110328
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Beta-Agonists And Death From Asthma (Correspondence)

  Woolcock, A.J.; Sears, M.R.; Barnes, P.J.; Staudinger, H.W.; Haas,
  J.F.; Gottlieb, Daniel J.; Celli, Bartolome R.; Pearce, Neil; Crane,
  Julian; Burgess, Carl; Beasley, Richard; Jackson, Rodney; Ernst,
  Pierre; Suissa, Samy; Boivin, Jean-Francois; Spitzer, Walter;
    rwitz, Ralph; Habbick, Brian; Cockcroft, Donald; McNutt, Mary;
  Buist, Sonia; Burrows, Benjamin; Lebowitz, Michael D.
  The New England Journal of Medicine
  Jul 30, 1992; 327 (5),pp 354-357
  LINE COUNT: 00231          WORD COUNT: 03200

 1/3/2
00109746
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The Use Of Beta-Agonists And The Risk Of Death And Near Death From Asthma
(Original Articles)

  Spitzer, Walter O.; Suissa, Samy; Ernst, Pierre; Horwitz, Ralph I.;
  Habbick, Brian; Cockcroft, Donald; Boivin, Jean-Francois; McNutt, Mary
  ; Buist, A. Sonia; Rebuck, Anthony S.
  The New England Journal of Medicine
  Feb 20, 1992; 326 (8),pp 501-506
  LINE COUNT: 00375          WORD COUNT: 05176
?t/9/2

 1/9/2
00109746
Copyright 1992 by the Massachusetts Medical Society

T  Use Of Beta-Agonists And The Risk Of Death And Near Death From Asthma
(  ginal Articles)

  Spitzer, Walter O.; Suissa, Samy; Ernst, Pierre; Horwitz, Ralph I.;
  Habbick, Brian; Cockcroft, Donald; Boivin, Jean-Francois; McNutt, Mary
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; Buist, A. Sonia; Reb[illegible]k, Anthony S.
The New England Journal of Medicine
Feb 20, 1992; 326 (8),pp 501-506
LINE COUNT: 00375 WORD COUNT: 05176
ISSN: 0028-4793
CORPORATE SOURCE: From the Department of Epidemiology and Biostatistics W.O.S., S.S., P.E., J.-F.B.) and the Department of Medicine, Montreal eneral Hospital (S.S., P.E.), McGill University, Montreal; the School of edicine, Yale University, New Haven, Conn. (R.I.H.); the Department of ommunity Health and Epidemiology (B.H.) and the Department of Medicine D.C.), University of Saskatchewan, Saskatoon, Sask., Canada; the H.E. obertson Laboratory, Laboratory and Disease Control Services Branch, askatchewan Health, Regina, Sask., Canada (M.M.); the Departments of edicine and Physiology, Oregon Health Sciences University, Portland A.S.B.); and the Division of Respiratory Medicine, Toronto Hospitals and he University of Toronto, Toronto (A.S.R.). Address reprint requests to r. Spitzer at McGill University, Purvis Hall, 1020 Pine Ave. W., Montreal, C H3A 1A2, Canada. - Supported by a grant from Boehringer-Ingelheim harmaceuticals, Canada, Ltd. Drs. Suissa and Ernst are research scholars f the Fonds de la Recherche en Sante du Quebec. Dr. Boivin is a National ealth Scholar of the National Health Research Development Program of ealth and Welfare Canada. At the time of the study, Dr. Spitzer was isiting National Health Scientist of Canada in the United Kingdom, upported by the National Health Research Development Program. - This study s based in part on data provided by the Saskatchewan Department of Health. he interpretations and conclusions contained herein do not necessarily epresent those of the Government of Saskatchewan or the Saskatchewan epartment of Health.

Abstract

Background. Morbidity and mortality from asthma appear to be ncreasing, and it has been suggested that medications used to treat asthma re contributing to this trend. We investigated a possible association etween death or near death from asthma and the regular use of beta(sub)-agonist bronchodilators.

Methods. Using linked health insurance data bases from Saskatchewan, anada, we conducted a matched case-control study of subjects drawn from a ohort of 12,301 patients for whom asthma medications had been prescribed etween 1978 and 1987. We matched 129 case patients who had fatal or ear-fatal asthma with 655 controls (who had received medications for sthma but had not had fatal or near-fatal events) with respect to region f residence, age, receipt of social assistance, and previous ospitalization for asthma.

Results. The use of beta-agonists administered by a metered-dose nhaler was associated with an increased risk of death from asthma (odds atio, 2.6 per canister per month; 95 percent confidence interval, 1.7 to .9) and of death or near death from asthma, considered together (odds atio, 1.9; 95 percent confidence interval, 1.6 to 2.4). For death from sthma, use of the beta-agonist fenoterol was associated with an odds ratio f 5.4 per canister, as compared with 2.4 for the beta-agonist albuterol. n a microgram-equivalent basis, the odds ratio for this outcome with enoterol was 2.3, as compared with 2.4 with albuterol.

Conclusions. An increased risk of death or near death from asthma was ssociated with the regular use of inhaled beta(sub 2)-agonist ronchodilators, especially fenoterol. Regardless of whether beta-agonists re directly responsible for these adverse effects or are simply a marker or more severe asthma, heavy use of these agents should alert clinicians hat it is necessary to reevaluate the patient's condition. (N Engl J Med 992;326:501-6.)

TEXT

1 April 1989, investigators from New Zealand reported the results of a ase-control study in which the use of fenoterol, a selective beta(sub)-agonist, was found to be associated with an increased risk of death from st a (Ref. 1). The study found no similar increase in risk for albuterol, ie other beta-agonist widely used in New Zealand. These findings igendered controversy, because the studies were considered subject to bias om several sources, including imbalances in the selection of controls and i the collection of data on exposure to bronchodilators, as well as adequate adjustment for differences in the severity of asthma.

In response to this concern, the investigators have reported the esults of two further case-control studies (Ref. 2,3). In these studies, ich minimized the bias due to the selection of controls and data ollection, an association with death from asthma was again found for enoterol, but not for albuterol. The controversy has been heightened by ie recent report that regular use of fenoterol, as compared with "as eeded" use, was associated with a deterioration in the control of asthma mptoms (Ref. 4). A major unresolved question was whether the associations bserved with the use of fenoterol were also present with other beta(sub -agonists.

The Saskatchewan Asthma Epidemiology Project was planned to address ny of these uncertainties (Ref. 5). Specifically, we asked whether egular, long-term use of beta-agonists in general, and of fenoterol in rticular, was associated with an increased risk of death or near death om asthma. In conducting this research, we used the health insurance data ases of the province of Saskatchewan, where the population of 1.1 million s insured for the cost of most hospital and ambulatory care and the cost f prescription drugs. The Saskatchewan data bases, which permit one to ink information from different sources for each person, have been es bed in detail elsewhere (Ref. 6,7).

Methods

Source and Eligibility of Study Subjects

We began by examining the computerized files of the Saskatchewan escription Drug Plan, which held just over 20 million prescriptions for ugs listed in the Saskatchewan formulary that had been dispensed to ligible residents of the province 5 to 54 years of age between 1980 and 987. Subjects outside this age range were not included because of the eater likelihood that drugs prescribed for them were for conditions other an asthma. We identified 68,813 beneficiaries of the plan who had eceived at least one prescription medication commonly used to treat asthma uring these years. These drugs were fenoterol, albuterol, metaproterenol, rbutaline, any compound of theophylline, ipratropium bromide, cromolyn, d inhaled beclomethasone. We then included all drugs prescribed for these tients during the period 1978 through 1987 and identified 12,301 patients r whom at least 10 prescriptions for one or more of the asthma drugs had en dispensed over the 10-year period. Within this geographically defined hort, we established the dates that further identified the available mbers of the cohort. The date on which each subject entered the cohort s defined as the date of the subject's 10th dispensed prescription, the bject's fifth birthday, or January 1, 1980, whichever was latest. The te of a subject's exit from the cohort was the subject's 55th birthday, ie date of the outcome event (death or near-fatal asthma), the date of the bject's emigration from the province, or April 30, 1987, whichever was rliest.

Outcomes and Identification of Case Patients

The case patients were subjects within the cohort who met edetermined criteria for near-fatal asthma or death from asthma during ie years 1980 through 1987. If a subject who died of asthma had previously d a near-fatal episode, the death was chosen as the outcome for analysis.

The primary hypothesis concerned the association of near deaths plus deaths, treated as a combined outcome measure, with exposure to any beta-agonist dispensed by a metered-dose inhaler.

We searched the data base to identify all the deaths among the 12,301 members of the cohort. Death certificates, coroners' reports, autopsy reports, and hospital-discharge summaries were obtained for all these deaths. Of 180 deaths identified, no documents were found for 15. Three physicians with special expertise in asthma reviewed all available information about the 165 deaths independently and categorized each as being probably due to asthma, possibly due to asthma, or not likely to be due to asthma. The consultants were blinded to the medications used and to the identity of the patients. They classified 44 deaths as probably due to asthma, reaching complete agreement independently for 40 of them and by consensus for the remaining 4.

Patients were classified as having near-fatal asthma if they had hypercarbia (arterial partial pressure of carbon dioxide above 6.0 kPa [45 mm Hg]), nonelective intubation during an acute asthma attack, or both. To identify episodes of asthma that might meet these criteria, we searched the data bases for procedure or billing codes corresponding to cardiopulmonary resuscitation, airway intubation, or assisted ventilation in hospitalized members of the cohort whose discharge diagnoses suggested airway disease (codes 490 to 493 and 496 of the International Classification of Diseases, 9th Revision, Clinical Modification) (Ref. 8). In addition, the medical charts of patients hospitalized for asthma for five days or more at six large referral hospitals were examined. For 99 percent of the hospitalizations of the 964 subjects with potential episodes of near-fatal asthma, hospital-discharge summaries and laboratory results were obtained. Eighty-five subjects were identified as having had one or more probable episodes of near-fatal asthma; the three consultants reached complete agreement independently for 80 of them and by consensus for the remaining 5. A subject's most recent near-fatal episode was used when more than one such episode was identified.

Selection of Controls

Up to eight controls for each case patient were selected randomly within the cohort after they were matched with respect to the following variables: region of residence, receipt of social assistance at any time during the study, age at entry into the cohort, date of entry, and hospitalization at least once in the two years before the event. In addition, the controls were required to have been at risk for the outcome at the time of the event in the case patient, a date we refer to as the index date.

Exposure to Asthma Medications

The principal risk factor examined was long-term use of inhaled beta(sub 2)-agonists delivered by a metered-dose inhaler. We defined long-term use as the use of a drug during the 12 months preceding the index date. The data base also permitted us to count accurately the number of prescriptions dispensed for any of the drugs under study, month by month. We therefore computed the number of units dispensed during the 12 months before the index date, with one unit defined as the amount of beta-agonist dispensed by one metered-dose inhaler per month. When a medication was dispensed as a dry powder or nebulizer solution, one unit was the dose usually prescribed per month. For the other asthma drugs (e.g., oral beta-agonists, theophylline, corticosteroids, and the like), one unit referred to an actual dispensed prescription.

Ascertainment of Adjustment Variables

Data on the use of health services and concomitant medications were obtained to adjust for possible differences between the case patients and the controls. The health insurance files for the case patients and the controls provided a record of their use of health services. From these files we calculated the number of hospitalizations for asthma for each

study subject and the number of visits to a physician in the two years before the index event. The use of drugs other than those to treat asthma was also established from the files of the prescription-drug plan. We grouped these drugs into four categories: (1) cardiac medications, including antihypertensive and potassium-sparing diuretic agents; (2) neurologic drugs, including anticonvulsants, antidepressants, and major tranquilizers; (3) drugs relatively contraindicated in asthma, specifically beta-blockers, sedatives, and parasympathomimetic agents; and (4) non-potassium-sparing diuretic agents. An index of risk was created, representing the number of categories of concomitant therapy received.

Statistical Analysis

We initially carried out a bivariate analysis that estimated crude matched odds ratios; in fact, these were adjusted for the four matching factors with use of conditional logistic regression (Ref. 9). Multiple conditional logistic regression for matched sets, (Ref. 10) with a variable number of controls per case patient, was used to estimate the adjusted odds ratios for the independent effects of the various asthma medications. The frequency of use, measured in units, of the two principal beta-agonists taken by metered-dose inhaler over the 12-month period, was quantified in three different ways. First, exposure was classified as being present or absent (a dichotomous variable). Second, exposure was categorized ordinally in the following four classes, according to the number of metered-dose inhalers used over the 12 months: 0, 1 to 12, 13 to 24, or 25 or more. Third, exposure was quantified as the number of units used per month, with the resulting continuous dose-response odds ratio measuring the increase in risk per unit per month. For the other asthma medications, we used both the dichotomous and the continuous classifications.

Because the only formulation of albuterol available in a metered-dose inhaler contained 100 microg per inhalation, as compared with 200 microg in each inhalation from the fenoterol inhaler, the odds ratios were also calculated with the assumption that one unit of fenoterol was equivalent to two units of albuterol. This was done by dividing the regression coefficients by 2, and since the logistic model used in the odds ratios was log-linear, the square root of the coefficient provided the appropriate estimate of effect.

The goodness of fit of the regression models, particularly the continuous dose-response model, was addressed in two ways. First, the assumption of log-linearity for the per-unit odds ratios was evaluated by comparing the fitted values from the continuous model with the values of the odds ratios estimated from the ordinal model. Second, the stability of the odds ratios was verified by assessing the effect of removing influential observations (Ref. 11). For all the results presented, the goodness-of-fit and stability evaluations of the regression models resulted in fluctuations of the estimated odds ratios of +/- 20 percent at most, well within the magnitude of the random error. Finally, some regression models were made parsimonious by removing variables that had no effect on the odds ratios of interest, thus improving their precision. Two-tailed 95 percent confidence intervals are provided for each odds ratio.

Peer Review

Because this study was funded entirely by Boehringer-Ingelheim Pharmaceuticals, which has a commercial interest in one of the products assessed, the investigators and the sponsor agreed on a verifiable peer-review process. Accordingly, a Scientific Advisory Board was created that reviewed the protocol in February 1990 after determinations of feasibility had been done, but before field work had begun. The chairman of the advisory board assessed and documented changes made in the interim by the investigators and circulated them to the entire board. The board reviewed the main results, conclusions, and interpretations of the data in June 1991.

Results

Table 1 shows selected characteristics of the study subjects. Overall, he case patients and the controls were similar with respect to age and ex. As compared with the controls, the case patients were hospitalized ore frequently and used the services of physicians more often. They also sed several classes of medications other than asthma drugs more often, a ifference that was more pronounced when only the subjects who died from sthma were considered. When concomitant medications were combined into an ggregate index, their use was more frequent among the case patients who ied of asthma (odds ratio, 2.2; 95 percent confidence interval, 1.0 to .9). In subsequent analyses, the odds ratios were adjusted for differences n the number of hospitalizations and in the index for the aggregate use of ther medications, but not for the number of visits to a physician, because his factor did not prove to be important in any analysis. *Table 1. elected Characteristics of Study Subjects Who Died of Asthma or Had ear-Fatal Asthma *. **TABLE OMITTED**

The relation between the use of asthma medications and the risk of atal or near-fatal asthma is shown in Table 2. In this table, frequencies f exposure to asthma medications are shown in an unmatched format for the ase patients and the controls, with unadjusted matched odds ratios alculated. In addition, odds ratios and 95 percent confidence intervals ere calculated by multivariate matched techniques, including adjustment or the use of other asthma medications, as well as for the number of ospitalizations and the index of use of concomitant medication. *Table 2. atched Odds Ratios for Exposure to Asthma Medication in the Subjects with atal or Near-Fatal Asthma, during the 12 Months before the Index Date *. *TABLE OMITTED**

In this analysis, the adjusted matched odds ratios indicated that both enoterol and albuterol taken by metered-dose inhaler were associated with n increased risk of death from asthma or near-fatal asthma, as well as ith an increased risk of death alone. An increased risk of death or ear-fatal asthma was also found for albuterol taken by nebulizer and for ther inhaled beta-agonists, theophylline, and oral corticosteroids. No ncrease in risk was noted for the use of inhaled corticosteroids and romolyn, considered together. The results were similar when deaths from sthma were considered alone, except that there was no increase in risk ssociated with the use of oral corticosteroids.

In the comparison of crude and adjusted matched odds ratios, an mportant point is apparent about the association between the use of nhaled albuterol and the risk of death from asthma. In Table 2, the crude atched odds ratio for albuterol was 0.9, but it increased to 2.8 after djustment for the use of fenoterol. As Table 3 shows, this increase ccurred because the odds ratio for albuterol was 1.2 among the patients ho also used fenoterol and 3.7 among those who did not. When the odds atio was calculated with adjustment for fenoterol use and other factors, he overall increase in risk for albuterol -- to an odds ratio of 2.8 Table 2) -- became clinically important and statistically significant. The ata in Table 3 also explain why previous studies found a spurious rotective odds ratio for albuterol. When the analysis was restricted to atients who used albuterol or fenoterol but not both, the crude odds atios were 3.7 for fenoterol and 0.3 for albuterol -- i.e., reciprocal atios. *Table 3. Relation of Albuterol Use to the Incidence of Death from sthma, with Adjustment for Use of Fenoterol *. **TABLE OMITTED**

Table 4 refines the analysis of the delivery of fenoterol and lbuterol by metered-dose inhaler by using an ordinal classification of xposure. In this analysis, the categories were the numbers of dispensed nits of either drug over a 12-month period (0, 1 to 12, 13 to 24, and 25 r more). When an odds ratio of 1.0 was assigned to the reference category f no use, the values for death from asthma and near-fatal asthma combined anged from 4.1 to 21.5 for fenoterol and were statistically significant. imilar results were found for albuterol. In the analysis of death from

sthma the drugs were comparable, except that there were higher odds ratios or fenoterol at higher levels of exposure. In this ordinal analysis of xposure, the increasing gradient in risk with increasing use of beta(sub)-agonists is clear. Patients who received more than two metered-dose nhalers per month on average had a very large excess risk of death or e fatal asthma or of death alone. Fenoterol was available only in doses f 200 microg per inhalation, and albuterol only in 100-microg doses. So hat the two medications can be compared on a weight-for-weight basis, able 4 also includes an ordinal analysis of exposure in which the number f inhalers of fenoterol was reduced by half. *Table 4. Adjusted Matched dds Ratios for Inhaled Fenoterol or Inhaled Albuterol in the Subjects with atal or Near-Fatal Asthma during the 12 Months before the Index Date, ccording to an Ordinal Classification of Exposure *. **TABLE OMITTED**

Table 5 shows the odds ratios for each additional unit of inhaled eta-agonists dispensed per month. As estimated from a regression model, he odds ratios for any inhaled beta-agonist were 1.9 for death and ear-fatal asthma and 2.6 for death alone. In a separate model, the odds atios for each unit of fenoterol were 2.3 for death and near-fatal asthma nd 5.4 for death only; for albuterol, the odds ratios were 1.9 and 2.4, espectively. *Table 5. Adjusted Matched Odds Ratios for Inhaled Fenoterol r Albuterol in the Subjects with Fatal or Near-Fatal Asthma during the 12 onths before the Index Date, According to Models of Continuous Exposure *. *TABLE OMITTED**

The analysis based on continuous exposure in Table 5 enabled us to ompare the use of 100 microg of fenoterol with the use of 100 microg of lbuterol. In this weight-for-weight analysis, the odds ratio for fenoterol as 1.5 for death and near death combined, similar to the odds ratio of 1.9 or albuterol. Similarly, for death alone, the odds ratio of 2.3 for enoterol was almost indistinguishable from the value of 2.4 for albuterol.

We also looked at the use of beta-agonists among subjects thought to e low risk. Among those not hospitalized for asthma in the previous two ea.s, the odds ratios for death from asthma remained significantly levated for both albuterol (2.4; 95 percent confidence interval, 1.3 to .7) and fenoterol (2.1; 95 percent confidence interval, 1.0 to 4.7).

In this cohort there were 47,842 person-years of follow-up. To stimate the absolute risks of death from asthma in a population of atients with asthma, we used the distribution of exposure in the 655 ontrols to approximate the person-time during which fenoterol and lbuterol administered by metered-dose inhaler were used (Ref. 12). The verall rate of death from asthma was 9.2 per 10,000 person-years (95 ercent confidence interval, 6.8 to 12.4). The rate for fenoterol was 34.6 95 percent confidence interval, 21.4 to 56.1), whereas the rate for lbuterol was 8.6 per 10,000 person-years (95 percent confidence interval, .9 to 12.6). For those not taking either of these two inhaled eta-agonists, the rate of death from asthma was 1.8 per 10,000 erson-years (95 percent confidence interval, 0.4 to 7.5). These absolute ates are crude and therefore unusable; any comparisons between them do not ake into account differences with respect to doses and other factors ssociated with the risk of death from asthma.

Discussion

In a case-control study of subjects drawn from a population-based ohort, we found that the use of inhaled beta-agonist bronchodilators, rincipally fenoterol and albuterol, was associated with an increased risk f the combined outcome of fatal and near-fatal asthma, as well as of death rom asthma alone.

When investigators earlier reported an increase in mortality from s a in various countries around the world, the explanations focused on ewly introduced treatments (Ref. 13). The case-control studies from New ealand emphasized the possible role of one particular bronchodilator, enoterol, while suggesting that other bronchodilators did not similarly

ncrease the risk of death from asthma (Ref. 1-3). Our study reveals that he use of beta-agonist drugs as a class, not just that of fenoterol alone, s associated with an increased risk of death from asthma. Furthermore, the se of theophyllines, another commonly used class of bronchodilators, was lso associated with an excess risk of a major adverse event. On the other and, the antiinflammatory agents cromolyn and inhaled corticosteroids were ot associated with such a risk.

An important advantage of our study was the availability of data on he number of metered-dose inhalers dispensed per month. These data ermitted detailed dose-response analyses for the two beta-agonist agents ost commonly used. The increased risk of fatal and near-fatal asthma with he use of albuterol and fenoterol was clinically important for patients ho used one to two canisters per month. For patients who used more than wo canisters monthly, both bronchodilators were associated with a greatly ncreased risk, which was especially marked for fenoterol.

At the time of the study, canisters of fenoterol in Saskatchewan ontained 200 inhalations, each of 200 microg of drug, whereas those of lbuterol contained 200 inhalations, each of 100 microg. Because different ormulations are available elsewhere (100 microg of fenoterol and 200 icrog of albuterol), we examined the risk associated with these two edications on a weight-for-weight basis. This analysis suggested a similar isk of death per 100 microg of either drug. The validity of such a eight-equivalence approach has been supported by in vitro (Ref. 14,15) and n vivo (Ref. 16,17) studies, as well as by clinical research (Ref. 18-20).

One limitation of our study was that the only data available with hich to adjust for the severity of asthma were those from the computerized lata bases. Fieldwork to collect relevant data from hospitals and hysicians in Saskatchewan may permit further adjustment for severity. hus, it remains plausible that many of the drugs for asthma appear to ncrease risk because the patients for whom asthma medications are rescribed are more likely to die from their more severe asthma. However, ven among subjects at low risk who were not hospitalized in the two years efore the index event, both albuterol and fenoterol were associated with a oubling of the risk of death from asthma. Furthermore, an increase in risk as much less apparent in the case of antiinflammatory asthma medications, hich one might expect would be added to the treatment of patients with ore severe disease that was not controlled with bronchodilator agents lone.

There are several possible explanations for the association between eta-agonists and death from asthma. We have already commented on the ikelihood that patients for whom asthma medications are prescribed have ore severe disease than other patients with asthma. A second possibility is that beta-agonists have adverse effects on organ systems other than the ungs. beta-Adrenergic agonists have long been under special scrutiny ecause of their potential for cardiotoxicity (Ref. 21) and their potential o induce hypokalemia (Ref. 22). A review of the available clinical information, however, suggests that at most 7 of the 44 deaths from asthma in our study might have been sudden and therefore possibly cardiac in rigin. Rapidly progressive respiratory failure was much more common, as as been recently suggested by others (Ref. 23).

Recent evidence suggests that beta(sub 2)-agonists may make asthma orse, (Ref. 4) perhaps by increasing airway hyperresponsiveness (Ref. 4-26). According to this explanation, beta-agonists are precursors of severe asthma, possibly leading to death, so that distinguishing the elative effects of the disease and of its treatment is difficult in bservational studies such as ours.

Clinicians should also remain alert to another possible mechanism, -- hat the benefits of beta(sub 2)-agonists for symptoms engender verreliance on this form of asthma management. If patients and their hysicians are misled by the control of symptoms into thinking that the

atient's underlying asth[redacted]is stable, necessary anti[redacted]flammatory treatment r other medications may be withheld while the patient's disease becomes ife-threatening. Severe attacks of asthma may also become the rule with he use of beta-agonists if sensitivity to bronchoconstrictive agents is e~~easedwhile maximal airway narrowing is maintained, and attacks may [illegible] more rapidly, as has recently been suggested (Ref. 27). Whatever the ature of the associations observed, whether they are causal relations or arkers of severity, heavy use of these medications should send a clear ignal to the patient and physician that the likelihood of a major adverse vent is markedly increased and that further evaluation is needed.

We are indebted to the following members of the Scientific Advisory oard for reviewing the protocol for this study and the final report: rofessors Peter Barnes (University of London), Bernard Begaud (University f Bordeaux), Nicholas Day (Cambridge University), Michael Hensley Newcastle University, Australia), Michel Ibrahim, chairman (University of orth Carolina), Helmuth Kewitz (Free University of Berlin), Albert Sheffer Harvard University), and Stephen Walter (McMaster University), to Peter urney (United Medical and Dental Schools-St. Thomas Hospital, University f London); and to many others whose dedication made this study possible, n particular Brenda Hemmelgarn, Lucie Blais, and Leah Lueck.

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#31

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Timothy J. Barberich and James W. Young

Serial No.: 07/896,725 Group Art Unit: 1205

Filed: June 9, 1992 Examiner: L. Schenkman

Title: METHOD FOR TREATING ASTHMA USING OPTICALLY PURE R(-) ALBUTEROL

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Record of Telephonic Interview

To: Hon. Commissioner of Patents and Trademarks
Washington, D.C. 20231

Dear Sir:

This is not an amendment, nor it is intended to be responsive to any official Action from the Patent and Trademark Office. Rather it is intended to make of record the substance of a telephonic interview between Examiner Schenkman and applicants' undersigned representative on August 3, 1993.

On August 2, 1993 applicants' representative telephoned Examiner Schenkman and requested the opportunity to discuss the Examiner's final rejection of June 7, 1993 and applicant's response thereto submitted July 23, 1993. Examiner Schenkman graciously agreed to call applicant's representative after he had received and read the response.

On August 3, 1993, Examiner Schenkman called applicant's representative and indicated that he had received and read the response, and that it was his intention nonetheless to maintain his rejection. He indicated that the basis of his rejection was the belief that when there are two enantiomers, the person of skill always expects that one will be more active. Applicants

pointed out that in the present case the art was not silent on what the person of skill ought to expect. The art, described in earlier responses and declarations provided by applicants, teaches that there is no advantage to isolating either pure isomer over the racemate for the purpose of enhancing potency.

Examiner Schenkman then stated his belief that the art showed that the R-isomer would have fewer side effects. Applicants' representative explained that none of the art, available at the time of filing of the application, taught that there would be any advantage to using either isomer for diminution of side effects. In fact, the combined teachings of the art were clear on the point that there would be no advantage to using pure R-albuterol.

The Examiner asked what the declaration of Gunnar Aberg showed. Applicants' representative explained that the declaration showed that sensitization to spasmogens is associated with S-albuterol, but not with R, and that therefore there was a previously unappreciated advantage to the resolution and use of pure R-albuterol. The Examiner inquired whether that wasn't what Morley and Chapman had shown. Applicants' representative agreed that was indeed what Morley and Chapman had shown, but that both of the Morley and Chapman references appeared subsequent to the filing date of the instant application and were therefore independently supportive of applicants' position.

Examiner Schenkman reiterated his position that a person of skill would still expect one isomer to be better than the other. Had applicants isolated an unknown enantiomer or had the enantiomers been difficult to separate, and applicants devised a separation, he believed that might provide allowable subject matter, but under the present circumstances he felt R-albuterol would be unpatentable to applicants. Applicants' representative

pointed out that the pending claims were not to R-albuterol, per se, but to a use of R-albuterol and suggested a Jepson-type claim of the format:

> "In a method of using albuterol to treat asthma, the improvement which comprises reducing side effects by administering R-albuterol in place of racemic albuterol."

Examiner Schenkman did not believe that this would address his concerns either, because the treatment of asthma was a known use and the R-isomer was known isomer. He indicated that issue had been reached on this point, and the interview was then concluded.

On August 4, 1993 applicants' representative telephoned Examiner Schenkman to cite a 1987 decision of the Board of Patent Appeals and Interferences (ex parte Ferrari), which was believed highly relevant to the Examiner's concerns about the patentability of known enantiomers. Ferrari had sought claims to (-)-moprolol. Moprolol was known to exist as a racemic mixture of enantiomers, and the art would have led one to expect that the (-) enantiomer would possess essentially all of the known antihypertensive activity. The inventors found an unexpected beneficial result relating to cardiac side effects for the (-) enantiomer. The Board held that the claims were patentable on the basis of an unexpected, improved side effect profile. A copy of that decision is enclosed herewith for the convenience of the Examiner.

Also included for the convenience of the Examiner is a copy of an article by Spitzer et al. [New England Journal of Medicine 326, 501-506 (1992)] which emphasizes the clinical and therapeutic importance of the hypersensitivity reaction associated with racemic albuterol namely that it appears to lead

to increased risk of death from asthma or near fatal asthma (page 6, third and fourth paragraph and page 8, fourth and fifth full paragraphs). The use of optically pure R-albuterol, as claimed by applicants, avoids this serious side effect. However, such use of R-albuterol is neither taught nor suggested by the prior art.

Respectfully submitted,

Philip E. Hansen
Agent for Applicants
Registration No. 32,700

Dated: August 4, 1993

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450 New Karner Road
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Albany, New York 12212-2695

Telephone: (518) 452-5600
Facsimile: (518) 452-5579

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

SERIAL NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
07/896,725	06/09/92	BARBARICH T	SPC89-

SCHENKMAN, L

12M2/0812

PATRICIA GRANAHAN
HAMILTON, BROOK, SMITH & REYNOLDS
TWO MILITIA DRIVE
LEXINGTON, MA 02173

EXAMINER	
ART UNIT	PAPER NUMBER
1205	32

DATE MAILED: 08/12/93

Below is a communication from the EXAMINER in charge of this application
COMMISSIONER OF PATENTS AND TRADEMARKS

ADVISORY ACTION

☑ THE PERIOD FOR RESPONSE:

☐ is extended to run _____ from the date of the Final Rejection

☑ continues to run 30 D. from the date of the Final Rejection.

☐ expires three months from the date of the final rejection or as of the mailing date of this Advisory Action, whichever is later. In no event however, will the statutory period for response expire later than six months from the date of the final rejection.

Any extension of time must be obtained by filing a petition under 37 CFR 1.136(a), the proposed response and the appropriate fee. The date on which the response, the petition, and the fee have been filed is the date of the response and also the date for the purposes of determining the period of extension and the corresponding amount of the fee. Any extension fee pursuant to 37 CFR 1.17 will be calculated from the date that the shortened statutory period for response expires as set forth above.

☐ Appellant's Brief is due in accordance with 37 CFR 1.192(a).

☑ Applicant's response to the final rejection, filed 8/5/93 has been considered with the following effect, but it is not deemed to place the application in condition for allowance:

1. ☐ The proposed amendments to the claim and/or specification will not be entered and the final rejection stands because:
   a. ☐ There is no convincing showing under 37 CFR 1.116(b) why the proposed amendment is necessary and was not earlier presented.
   b. ☐ They raise new issues that would require further consideration and/or search. (See Note).
   c. ☐ They raise the issue of new matter. (See Note).
   d. ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal.
   e. ☐ They present additional claims without cancelling a corresponding number of finally rejected claims.

   NOTE: _____

2. ☐ Newly proposed or amended claims _____ would be allowed if submitted in a separately filed amendment cancelling the non-allowable claims.

3. ☐ Upon the filing of an appeal, the proposed amendment ☐ will be ☐ will not be, entered and the status of the claims in this application would be as follows:

   Allowed claims: _____
   Claims objected to: _____
   Claims rejected: _____
   However,
   a. ☐ The rejection of claims _____ on references is deemed to be overcome by applicant's response.
   b. ☐ The rejection of claims _____ on non-reference grounds only is deemed to be overcome by applicant's response.

4. ☑ The affidavit, exhibit or request for reconsideration has been considered but does not overcome the rejection.

5. ☐ The affidavit or exhibit will not be considered because applicant has not shown good and sufficient reasons why it was not earlier presented.

☐ The proposed drawing correction ☐ has ☐ has not been approved by the examiner.

☐ Other The Fenton dilution is not controlling since the examiner points a different activity than the activity cited in the racemic mixture. Also the prior cited art (e.g. Hartley et al) discloses increased activity (primary) of the R(-) isomer. No further amendment will be considered

Leonard Schenkman
LEONARD SCHENKMAN
PRIMARY EXAMINER
GROUP 1200

PTOL-303 (REV 3-86)

DLEV012241

Exp. ap -217-Rq125

P.Gal #33 1-5-94

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Barberich et al.

Serial No. 07/896,725 Group Art Unit: 1205

Filed: June 9, 1992 Examiner: Schenkman

Title: METHOD FOR TREATING ASTHMA USING OPTICALLY PURE R(-) ALBUTEROL

REQUEST FOR EXTENSION OF TIME
37 CFR §1.136(a)

Hon. Commissioner of Patents and Trademarks
Washington, D.C. 20231

Dear Sir:

Applicant hereby requests an extension of three (3) months for filing a Response to an Office Action dated June 7, 1993. A check in the amount of $420 to cover this request is enclosed. The Commissioner is hereby authorized to charge payment of any fees associated with this communication or credit any overpayment to Deposit Account No. 08-1935.

Respectfully submitted,

Philip E. Hansen
Agent for Applicant
Reg. No. 32,700

Dated: December 7, 1993

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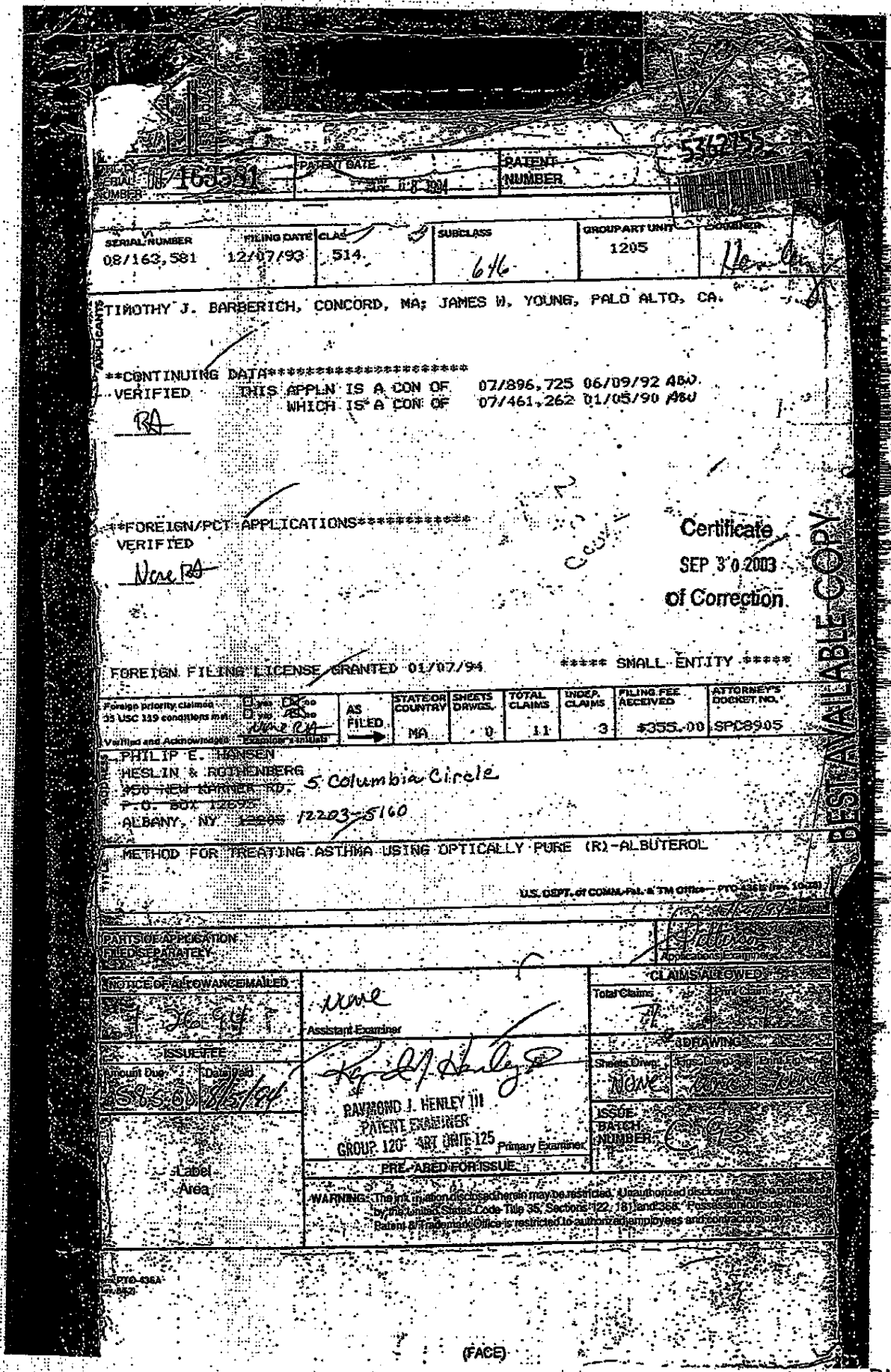
090 BA 12/23/93 07896725 1 217 420.00 CK



[redacted]

5342255

APPLICATION SERIAL NUMBER 08/163581 | PATENT DATE JUN 6 1994 | PATENT NUMBER

SERIAL NUMBER	FILING DATE	CLASS	SUBCLASS	GROUP ART UNIT	EXAMINER
08/163,581	12/07/93	514	646	1205	None

APPLICANT: TIMOTHY J. BARBERICH, CONCORD, MA; JAMES W. YOUNG, PALO ALTO, CA.

CONTINUING DATA********
VERIFIED THIS APPLN IS A CON OF 07/896,725 06/09/92 ABD.
WHICH IS A CON OF 07/461,262 01/05/90 ABD
RA

FOREIGN/PCT APPLICATIONS********
VERIFIED
None RA

Certificate
SEP 30 2003
of Correction

FOREIGN FILING LICENSE GRANTED 01/07/94 ***** SMALL ENTITY *****

Foreign priority claimed 35 USC 119 conditions met	Verified and Acknowledged Examiner's Initials	AS FILED	STATE OR COUNTRY	SHEETS DRWGS.	TOTAL CLAIMS	INDEP. CLAIMS	FILING FEE RECEIVED	ATTORNEY'S DOCKET NO.
Yes No / Yes No	None RA	→	MA	0	11	3	$355.00	SPC8905

PHILIP E. HANSEN
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~~900 NEW KARNER RD.~~ 5 Columbia Circle
~~P.O. BOX 12675~~
ALBANY, NY ~~12208~~ 12203-5160

METHOD FOR TREATING ASTHMA USING OPTICALLY PURE (R)-ALBUTEROL

U.S. DEPT. of COMM.-Pat. & TM Office—PTO-436 (Rev. 10-78)

PARTS OF APPLICATION FILED SEPARATELY

Applications Examiner

NOTICE OF ALLOWANCE MAILED

Assistant Examiner: None

CLAIMS ALLOWED: Total Claims — Print Claim

ISSUE FEE: Amount Due — Date Paid: $880.00 8/5/94

DRAWING: Sheets Drwg. NONE — Figs. Drawn — Print Fig.

RAYMOND J. HENLEY III
PATENT EXAMINER
GROUP 120 ART UNIT 125 Primary Examiner

ISSUE BATCH NUMBER

PRE-AIRED FOR ISSUE

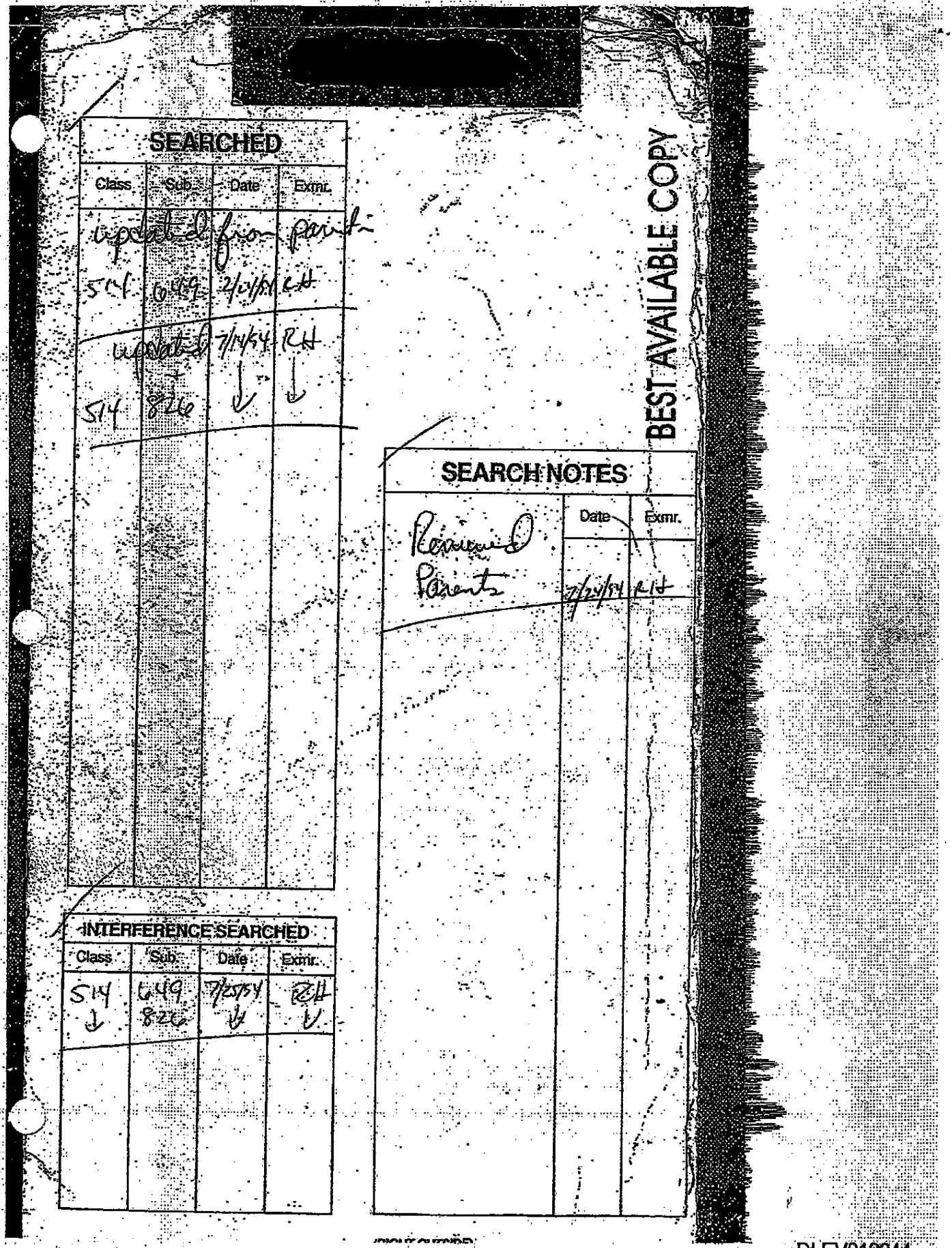
Label Area

WARNING: The information disclosed herein may be restricted. Unauthorized disclosure may be prohibited by the United States Code Title 35, Sections 122, 181 and 368. Possession outside the Patent & Trademark Office is restricted to authorized employees and contractors only.

PTO-436A (FACE)

BEST AVAILABLE COPY

DLEV012243



SEARCHED

Class	Sub.	Date	Exmr.
updated from parent			
514	649	2/24/54	RH
updated		7/14/54	RH
514	826	↓	↓

SEARCH NOTES

	Date	Exmr.
Reviewed Parents	7/24/54	RH

INTERFERENCE SEARCHED

Class	Sub.	Date	Exmr.
514 ↓	649 826	7/25/54 ↓	RH ↓

BEST AVAILABLE COPY

Staple Issue Slip Here

POSITION		ID NO.	DATE
CLASSIFIER			
EXAMINER		405	1-5-94
TYPIST		323	1/7
VERIFIER		352	1-8-94
CORPS CORR.			
SPEC. HAND			
FILE MAINT.			
DRAFTING			

INDEX OF CLAIMS

Claim	Date
Prior	
Original	12/30 12/31
1	✓
2	
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5	✓
6	✓
7	✓
8	
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12	✓
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15	✓
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Claim	Date
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SYMBOLS

✓ — Rejected
– — Allowed
- (Through numeral) — Cancelled
R — Restricted
N — Non-elected
I — Interference
A — Appeal
O — Objected

(LEFT INSIDE)

OMB No. 0651-0011 (12/31/88)

08/163581

DOCKET NUMBER	ANTICIPATED CLASSIFICATION OF THIS APPLICATION: CLASS	SUBCLASS	PRIOR APPLICATION: EXAMINER	ART UNIT
RC89-05			L. Schenkman	1205

ess to: Commissioner of Patents and Trademarks
Box FWC
Washington, D.C. 20231

This is a Request for filing a ☐ continuation-in-part ☒ continuation ☐ divisional application under 37 CFR 1.62 of prior application Serial No. 07/896,725, filed on 6-9-92 entitled METHOD FOR TREATING ASTHMA USING OPTICALLY PURE (R)-ALBUTEROL by the following named inventor(s).

FULL NAME OF INVENTOR	FAMILY NAME: Barbera ch - 1-P	FIRST GIVEN NAME: Timothy	SECOND GIVEN NAME: J.
RESIDENCE & CITIZENSHIP	CITY: Concord	STATE OR FOREIGN COUNTRY: Massachusetts MA	COUNTRY OF CITIZENSHIP: United States
POST OFFICE ADDRESS	POST OFFICE ADDRESS: 73 Nashoba Road	CITY: Concord	STATE & ZIP CODE/COUNTRY: MA 01742/U.S.A.
FULL NAME OF INVENTOR	FAMILY NAME: Young 2-P	FIRST GIVEN NAME: James	SECOND GIVEN NAME: William
RESIDENCE & CITIZENSHIP	CITY: Palo Alto	STATE OR FOREIGN COUNTRY: California Ca	COUNTRY OF CITIZENSHIP: United States
POST OFFICE ADDRESS	POST OFFICE ADDRESS: 765 Talisman Court	CITY: Palo Alto	STATE & ZIP CODE/COUNTRY: CA 94303/U.S.A.
FULL NAME OF INVENTOR	FAMILY NAME:	FIRST GIVEN NAME:	SECOND GIVEN NAME:
RESIDENCE & CITIZENSHIP	CITY:	STATE OR FOREIGN COUNTRY:	COUNTRY OF CITIZENSHIP:
POST OFFICE ADDRESS	POST OFFICE ADDRESS:	CITY:	STATE & ZIP CODE/COUNTRY:

The above identified prior application in which no payment in the issue fee, abandonment of, or termination of proceedings has occurred, is hereby expressly abandoned as of the filing date of this new application. Please use all the contents of the prior application file wrapper, including the drawings, as the basic papers for the new application. (note: 37 CFR 1.60 may be used for applications where the prior application is not to be abandoned.)

1. ☐ Enter the amendment previously filed on _____ under 37 CFR 1.116 but unentered, in the prior application.

2. ☐ A preliminary amendment is enclosed.

The filing fee is calculated on the basis of the claims existing in the prior application as amended at 1 and 2 above.

Claims	(1) For	(2) Number filed	(3) Number extra	(4) Rate	(5) Calculations
	Total Claims	11 — 20=	- 0 -	X $22.00	$ - 0 -
	Independent Claims	3 — 3=	- 0 -	X $74.00	- 0 -
	Multiple Dependent Claim(s) (if applicable)			+$ 230.00	- 0 -
			Basic Fee		+ $ 710.00
			Total of above Caculations =		710.00
	Reduction by 1/2 for filing by small entity (Note 37 CFR 1.9, 1.27, 1.28) if applicable, affidavit must be filed also				— 355.00
			Total National Fee		$ 355.00

DLEV012246

3. ☒ The Commissioner is hereby authorized to charge fees under 37 CFR 1.16 and 1.17 which may be required, or credit any overpayment to Deposit Account No. 08-1935

4. ☒ A check in the amount of $ 355.00 is enclosed.

5. ☐ A new oath or declaration is included since this application is a continuation-in-part which discloses and claims additional matter.

6. ☒ Amend the specification by inserting before the first line the sentence:

This application is a ☐ continuation-in-part, ☒ continuation, ☐ division, of application Serial No. 07/896,725, filed 6/9/92 now abandoned. * still in effect.

7. ☐ A verified statement claiming small entity status is ~~enclosed or was filed in the prior application~~.

8. ☐ Priority of application Serial No. _____ filed on _____ in _____ is claimed under 35 U.S.C. 119.

9. ☒ The prior application is assigned of record to Sepracor, Inc.

10. ☐ The power of attorney in the prior application is to: Hamilton, Brook, Smith and Reynolds, P.C.; Associate Power of Attorney to Philip E. Hansen filed July 14, 1993

11. ☒ Also enclosed Express Mail Certificate

Address all future communications to: (May only be completed by applicant, or attorney or agent of record)

Philip E. Hansen, Heslin & Rothenberg, P.C.

450 New Karner Road, P.O. Box 12695

Albany, New York 12205

It is understood that secrecy under 35 U.S.C. 122 is hereby waived to the extent that if information or access is available to any one of the applications in the file wrapper of a 37 CFR 1.62 application, be it either this application or a prior application in the same file wrapper, the Patent and Trademark Office may provide similar information or access to all the other applications in the same file wrapper.

December 7, 1993
Date

Philip E. Hansen
Signature

Philip E. Hansen, Reg. No. 32,700

☐ inventor(s)
☐ assignee of complete interest
☒ attorney or agent of record
☐ filed under §1.34(a)

08/169301

CERTIFICATE OF MAILING BY "EXPRESS MAIL"

In the Application of: Barberich et al.

METHOD FOR TREATING ASTHMA USING OPTICALLY PURE (R)-ALBUTEROL

Attorney Docket No.: 0701.027B

"EXPRESS MAIL" MAILING LABEL NO. TB321785882US

Date of Deposit December 7, 1993

I hereby certify that this paper is being deposited with the U.S. Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and addressed to Commissioner of Patents and Trademarks, Box FWC, Washington, D.C. 20231.

Rita F. Palumbo
(Typed or printed name of person mailing paper or fee)

Rita F. Palumbo
(Signature of person mailing paper or fee)

PATENT APPLICATION FEE DETERMINATION RECORD

Effective October 1, 1992

Application or Docket Number: 163581

CLAIMS AS FILED - PART I

	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY RATE	SMALL ENTITY FEE	OR	OTHER THAN SMALL ENTITY RATE	OTHER THAN SMALL ENTITY FEE
FOR							
BASIC FEE				$355.00	OR		$710.00
TOTAL CLAIMS	11 minus 20 =	*	x$11=		OR	x$22=	
INDEPENDENT CLAIMS	3 minus 3 =	*	x 37=		OR	x 74=	
MULTIPLE DEPENDENT CLAIM PRESENT			+115=		OR	+230=	
			TOTAL	355	OR	TOTAL	

* If the difference in column 1 is less than zero, enter "0" in column 2.

CLAIMS AS AMENDED - PART II

AMENDMENT A

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE	SMALL ENTITY ADDITIONAL FEE	OR	OTHER THAN SMALL ENTITY RATE	OTHER THAN SMALL ENTITY ADDITIONAL FEE
Total	*	Minus	**	=	x$11=		OR	x$22=	
Independent	*	Minus	***	=	x 37=		OR	x 74=	
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM					+ 115=		OR	+230=	
					TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

AMENDMENT B

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE	ADDITIONAL FEE	OR	RATE	ADDITIONAL FEE
Total	*	Minus	**	=	x$11=		OR	x$22=	
Independent	*	Minus	***	=	x 37=		OR	x 74=	
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM					+ 115=		OR	+ 230=	
					TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

AMENDMENT C

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE	ADDITIONAL FEE	OR	RATE	ADDITIONAL FEE
Total	*	Minus	**	=	x$11=		OR	x$22=	
Independent	*	Minus	***	=	x 37=		OR	x 74=	
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM					+115=		OR	+230=	
					TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

FORM PTO-875 (Rev.10-92)

Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

DLEV012249

PATENT APPLICATION SERIAL NO. 08/163581

U.S. DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE
FEE RECORD SHEET

070 TH 12/21/93 08163581 1 201 355.00 CK 0701.027B

PTO-1556
(5/87)

DLEV012250

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Timothy J. Barberich and James W. Young

Applicant's Docket No.: SPC89-05 Group Art Unit: 1205

Filed: Examiner:

Title: METHOD FOR TREATING ASTHMA USING OPTICALLY PURE R(-) ALBUTEROL

To: Hon. Commissioner of Patents and Trademarks
Washington, D.C. 20231

PRELIMINARY REMARKS

Dear Sir:

This application is a file wrapper continuation of our earlier application, serial number 07/896,725 which is itself a continuation of application serial number 07/461,262.

Status of Claims

Claims 1 to 12 were presented in the '262 case as originally filed. Claims 7, 10, 11 and 12 were canceled and claims 13 and 14 were added in the response of September 23, 1991 in the '262 case. Claims 9, 13 and 14 were canceled and claims 15, 16, 17 and 18 were presented in the response of February 10, 1993 in the '725 case. Claims 1 to 6, 8 and 15 to 18 are therefore presently pending in the application. Three of these are independent claims (claims 1, 6 and 15).

All of the claims were rejected in the final action of June 7, 1993 (paper number 26) and the rejection was maintained in two subsequent advisory actions (papers 30 and 32). Thus, the status of the claims at the end of prosecution in the parent ('725) case was as follows:

Allowed Claims	Claims Objected To	Claims Rejected
None	None	1 to 6, 8, 15 to 18

Status of Amendments

An amendment was proffered in applicants' response of July 23, 1993, but it was not entered. The amendment is not believed necessary for further prosecution and has not been subsequently presented.

Summary of the Invention

Applicants' invention is directed to a method of treating asthma and reducing the undesirable side effects associated with racemic albuterol by using the R isomer of albuterol substantially free of the S isomer. R-albuterol may be combined with a bronchodilator, antihistamine or analgesic. Methods and pharmaceutical compositions relating to the combination also fall within the inventive concept.

The administration of β-agonists for the treatment of asthma is commonly accompanied by undesirable side effects. Evidence suggests that β_2-agonists may make asthma worse, perhaps by increasing airway hyperresponsiveness to spasmogens. This gives rise to the most serious of the side effects associated with the use of β-agonists to treat asthma: death from asthma. In this regard, Spitzer et al. [New England Journal of Medicine 326, 501-506 (1992)] have shown that racemic albuterol, taken by metered dose inhaler, was associated with an increased risk of death from asthma or near fatal asthma. When the odds ratio was calculated with adjustment for all factors, the increase in risk (to an odds ratio of 2.8) was clinically important and statistically significant.

Applicants have surprisingly found that, with regard to hypersensitivity, there is an unexpected advantage to the use of the pure R isomer. Applicants have shown (see the declaration of Gunnar Aberg accompanying the response of July 23, 1993) that the S isomer causes a hypersensitivity to allergen and that the desired bronchodilator effect due to the R isomer is prone to tachyphylaxis (desensitization), whereas

the undesired hypersensitivity arising from the S isomer is less prone to tachyphylaxis. This means that, in order to achieve bronchodilation, a patient in chronic treatment requires ever-increasing doses of racemic albuterol. While greater and greater doses of R-albuterol are needed to provide the desired bronchodilation, the accompanying greater and greater doses of S-albuterol dramatically increase the patient's susceptibility to asthmatic attack. Similar results have appeared, subsequent to applicants' invention, in two independent publications from other labs [Morley et al., British Journal of Pharmacology, 104, Supplement, 295P (1991) and Chapman, et al. Tran. In Pharm. Science 13, 231-232 (1992)]. Thus, by eliminating the S-isomer and its undesirable hypersensitization, applicants have found an unexpected benefit to the use of the pure R isomer for the treatment of asthma.

Issues

1. In the office action of June 7, 1993, a final rejection in the parent case, the examiner rejected claims 1 to 6 and 15 to 18 over Chemical Abstracts 89:123259m for "reasons of record." The reasons of record are found in the office action of August 20, 1990, in which the examiner states that the reference teaches the use of albuterol to treat asthma and that it is his position that the determination of a particular isomer to employ would be a matter of obvious alternatives to one skilled in the art.

2. The examiner also rejected claims 1 to 5 as unpatentable under 35 U.S.C. §103 over Brittain et al. [Brit. J. Pharmacol. 48, 144-147 (1973)], Hartley et al. [J. Med. Chem. 14, 895 (1971)] and Buckner et al. [JPET 189, 616-625 (1974)]. These references are relied upon to teach "the greater bronchodilation activity of the R isomer over the S isomer."

3. Claims 6, 8 and 15 to 18 were rejected under 35 U.S.C. §103 as obvious over Brittain et al, Hartley et al, and

Buckner et al, as before and further in view of Chemical Abstracts "for reasons of record." There is no "record" with regard to claims 15 to 18, which were newly presented in the response immediately preceding the rejection. One assumes from analogy to earlier office actions that the examiner takes the position that the Brittain, Hartley and Buckner references teach greater bronchodilation activity of the R isomer, and that the Chemical Abstracts reference teaches albuterol in combination with other drugs.

4. The examiner's position is that the declaration under 37 C.F.R. 1.132 of Gunnar Aberg of July 23, 1993 "failed to show unexpected activity or less undesirable side effects (e.g. comparative therapeutic indices)."

5. The examiner cited the case of *In re Adamson* [125 USPQ 233] for the proposition that a showing of unexpected activity in a Rule 132 declaration might not overcome his obviousness rejection.

Argument

Issue 1 - The rejection of claims 1 to 6 and 15 to 18 over Chemical Abstracts 89:123259m.

The Chemical Abstracts reference is directed to a comparison of bronchodilator effects of racemic albuterol and drug combinations incorporating racemic albuterol. The reference does not teach or suggest the use of an optically pure isomer of albuterol either alone or in combination. Arguably, the reference teaches away from the use of a single isomer to reduce side effects: it states, "a combination of salbutamol [albuterol] and hydroxyzine seems, therefore, to be one rational means of treating asthma with fewer side effects than the salbutamol-hydroxyzine-theophylline mixture, but still about the same effectiveness." Thus, the goal of the reference appears to be to lower the side effects associated with albuterol. However, rather than separate the enantiomers and use one enantiomer, as taught by applicants, (which the

examiner has alleged would be obvious) the authors turned instead to modulating components of the mixture.

The examiner's position that "the determination of a particular isomer to employ would be a matter of obvious alternatives" is only true if it is obvious that the use of a single isomer provides an advantage. That teaching is entirely missing from the reference. In this regard, it is worth noting that the mere fact that enantiomers exist does not render the use of a particular enantiomer obvious. In order to use an enantiomer, one must first prepare or isolate the single pure enantiomer. Because chemical resolution of a racemic mixture is never 100% efficient, a resolution will always yield less than 50% of the single isomer. Chiral syntheses are similarly expensive and/or inefficient. As stated by others (e.g., European patent application 256586, page 2, line 8) "a major reason for the continued use of mixtures of stereoisomers is that the cost of separation of the stereoisomers exceeds the potential advantage of a possible increase in activity." It would not have been obvious to prepare and use optically pure R-albuterol because there is no suggestion of any advantage of R-albuterol in the reference.

Issue 2 - The rejection of claims 1 to 5 as obvious over Brittain et al., Hartley et al. and Buckner et al.

Brittain et al. show that both enantiomers and the racemic mixture of albuterol are very selective for β_2 receptors, but the isomeric activity ratio of R- and S-albuterol on isolated tracheal muscle (β_2) vs atrial muscle (β_1) is "impossible to calculate...because the isomers are virtually inactive on this tissue." The potency ratio of R(-) vs racemic albuterol in β_2 receptors as measured by acetylcholine-induced bronchospasm in anesthetized guinea pigs is 1.28, in acetylcholine-induced pulmonary resistance in anesthetized dogs is 2.3 and on isolated guinea pig trachea is

0.90 (i.e. the racemate is 1.1 times as potent as the R isomer). Thus, from a study of the Brittain reference one may conclude nothing definitive regarding either the selectivity of R vs racemic or of the potency of R vs racemic.

Hartley and Middlemiss teach that both isomers and the racemic mixture of albuterol act on β_2 receptors rather than β_1 receptors. The effects of the R isomer and the racemic mixture are equiactive on β_2 receptors of the intact guinea pig trachea and indeed the racemate is reported to be 1.5 times as potent as the R isomer. There is no clear teaching with regard to selectivity between β_1 and β_2-receptors, which might indicate the potential for side effects. Thus no conclusion can be drawn from Hartley and Middlemiss as to whether the R isomer would enjoy any advantage over racemic albuterol in terms of side effects.

The study by Buckner and Abel examines the ratio of activity of the R and S isomers of albuterol in guinea pig atria and guinea pig trachea. They concluded "even though the potencies of single isomers may differ as much as twenty-four fold between atria and trachea, the stereoselectivity for production of activity is the same." That is, the selectivity, as measured by the ratio of tracheal to atrial activity, is the same for the two isomers. Buckner did not examine racemic albuterol, so no conclusion can be drawn as regards any potency advantage of a single pure R isomer vs the racemate.

In an earlier office action (December 9, 1991) the examiner had rejected the same claims over an additional reference by Hawkins et al. [J. Med. Chem. 16, 856-857 (1973)]. Although the rejection over Hawkins was not maintained in the final office action, it appears pertinent to the substance of the rejection, which might otherwise lack a balanced consideration of the art. In their studies, Hawkins et al. found that the R enantiomer was 2.15 times as potent as the racemate. They did not examine any tissue other than guinea pig trachea so that no conclusion relating to relative

selectivity could be drawn.

The issue of patentability must be approached "in terms of what would have been obvious to one of ordinary skill in the art at the time the invention was made in view of the sum of all of the relevant teachings in the art ..." [*In re Kuderna* (165 USPQ 575)]. There are two teachings that could have rendered the use of R-albuterol obvious: (1) a teaching that it is more than twice as potent as the racemate (which would indicate that the S-isomer's activity is antagonistic to the R-isomer's potency); or (2) a teaching that fewer side effects are associated with the R isomer. Neither of these teachings is found in any of the references. However, the art is not silent on what the person of skill ought to expect; it teaches that there is nothing to be gained, either in potency or side effects, by resolving the racemic albuterol. Hawkins et al. and Buckner et al. appear to indicate that the R isomer is about twice as potent as the racemate (which merely indicates that the S-isomer is inert); Hartley et al. teaches that the racemate is about 1.5 times as potent as the R isomer (which would indicate that the S-isomer has some therapeutic potency); Brittain et al. indicates that one or the other isomer is more potent, depending on the test. There is a certain lack of agreement among the references concerning the relative potency of the R isomer and the racemate, and the person of ordinary skill in the art would be, at least, confused by the cited references.

If one ignores some of the references, it appears that the R isomer may enjoy a theoretical twofold potency advantage over the racemate. However, even assuming that R-albuterol is twice as potent as the racemate, this would not motivate a person of skill and experience in the pharmaceutical industry to prepare and administer the pure R isomer. This is because, as discussed above, a process for the resolution of racemic albuterol would inevitably produce R-albuterol in less than 50% yield, whereas assuming that S-albuterol is totally inert ballast, the use of the racemic albuterol would, at worst,

provide 50% of the potency of the pure R. Thus there is nothing to be gained by resolving the racemate. A potency ratio significantly greater than two between a single enantiomer and its racemate would be consistent with antagonism by one enantiomer and would provide motivation for resolving the racemate. However, no such teaching is found in any of the references, even when viewed selectively. Therefore at the time of filing, the art did not, on the basis of potency, suggest any practical advantage to using pure R albuterol.

A second basis for separating enantiomers would be to provide lessened side effects. Indeed, the unexpected diminution in side effects when the pure R isomer of albuterol is administered is the basis of the instant application, but it is not suggested by any of the references. As explained in the July 23, 1993 declaration of Gunnar Aberg, side effects of drugs that have a predominant β_2 agonist component can arise from four presently recognized interactions: (a) non-adrenergic effects; (b) interaction of the β-agonist with α-receptors; (c) interaction of the β_2 agonist with β_1 receptors; and (d) interaction of the β_2 agonist with β_2 receptors.

(a) Non-adrenergic effects can be triggered by interaction with any of the hundreds of other receptors and by non-receptor interactions, and they can originate from portions of the drug molecule outside the β_2 pharmacophore. They are, for this reason, difficult to predict or screen for. Applicants are aware of no teachings in the literature of relative liabilities of racemate or enantiomers of albuterol as regards non-adrenergic effects, and theoretically such differences would be improbable.

(b) Interaction of β-agonists with α-receptors are known in first generation adrenergics but are not generally of clinical significance in second generation agonists like albuterol. Likewise,

applicants are aware of no art that would suggest any distinction between racemate and enantiomers on this basis.

(c) The interaction of β_2 agonists with β_1 receptors, causing pulmonary agents to exhibit cardiac side effects, is well documented and has been discussed above for Brittain, Hartley, Buckner and Hawkins. The literature cited provides no evidence for an advantage of either enantiomer of albuterol on the basis of β_1 vs. β_2 specificity.

(d) The fourth interaction, β_2 agonists acting at β_2 receptors giving rise to tachyphylaxis and sensitization, is known but not described in any of the references cited for albuterol.

Thus, in January of 1990 when the grandparent of the present application was filed, there was no teaching in the art that the use of pure R-albuterol enjoyed any advantage in diminution of side effects.

Issue 3 - The rejection of claims 6, 8 and 15 to 18 over Brittain et al, Hartley et al, Buckner et al and Chemical Abstracts.

The inadequacy of Brittain, Hartley and Buckner to support the rejection of applicants' claims to the use of R-albuterol has been presented above. The addition of the Chemical Abstracts reference, while indicating that racemic albuterol has been used with other drugs, does not supply the missing teaching regarding the advantage of the use of the R isomer in diminishing side effects.

Issue 4 - The setting aside of the Declaration of Dr. Gunnar Aberg.

Accompanying the response of July 23, 1993, applicants provided a declaration from Dr. Gunnar Aberg to establish that

his results and those of Chapman and of Morley would indicate to the person of skill in the art that the R isomer would have a higher therapeutic index in humans than would the racemate. Dr. Aberg averred that the tests relied on as evidence are accepted in the art as being predictive of efficacy in treating humans; the pending method of use claims are narrowly drawn to the specific use for which the tests are predictive. [See Ex parte Chwang (231 USPQ 751).] Dr. Aberg's credentials were presented in the declaration and his conclusions as to side effects and unexpected activity cannot be set aside by the examiner without some basis for so doing. None was presented. Therefore it is presumed that the declaration is accepted for what it teaches; namely, that a person of skill in the art would accept the studies in guinea pig trachea and the experiments of Chapman et al. and Morley et al. (described below) as predictive of a higher therapeutic index for R-albuterol. Applicants believe that the examiner's position that the declaration "failed to show unexpected activity or less undesirable side effects" cannot be maintained.

Dr. Aberg described experiments carried out in his laboratory in which isolated tracheal muscle preparations were subjected to graded doses of a spasmogen. It was found that the contractile response to the spasmogen was significantly increased in bronchial tissue strips that had been incubated with S-albuterol. No such effect was seen in the tissues that had been incubated with R-albuterol. Dr. Aberg concluded that the increased sensitivity to spasmogens from treatment with S-albuterol was due to a direct effect on bronchial smooth muscle.

Subsequent to the filing of applicants' original application, Morley et al. (op. cit.) and Chapman et al. (op. cit.) independently disclosed that the S isomer in bronchial tissue causes a hypersensitivity to allergen. Chapman et al. stated, "It has long been recognized that the use of sympathomimetics for asthma therapy is associated with a range

of inconsistent or frankly paradoxical effects...our findings indicate that it may be prudent to remove enantiomers that were previously thought to be biologically inert." Thus Morley and Chapman came to the same conclusion as applicants' original disclosure, and did so with the same understanding of the prior art as a whole: namely, that no expectation of an improved side effect profile was previously attached to the use of a single enantiomer.

In the period since the final office action of June 7, 1993 in the parent case, additional support for the conclusions drawn in the Aberg declaration has come to the attention of applicants. British patent application 2,255,503, filed more than a year after applicants' '262 application, discloses that the long standing problems inherent in therapy with albuterol and other β_2 sympathomimetic bronchodilators may unexpectedly be ameliorated by the expedient of administering the drug not, as hitherto, in the form of a racemic mixture, but as the R isomer (page 8, line 25 to line 33 of the copy enclosed). The problems that may be avoided are enumerated on page 12. A series of experiments is disclosed at page 15 to page 16 in which guinea pigs were challenged with intravenous histamine after intravenous infusion of S-albuterol or vehicle. The results indicated a profound hypersensitivity induced by S-albuterol. The British application comes to the same conclusion as did Dr. Aberg in his declaration: subjects receiving R-albuterol will exhibit a lessened tendency to hyperreactivity with equivalent benefit in terms of bronchodilator action (see page 24, line 3 to line 8 of GB 2,255,503).

This evidence of unexpected activity cannot, as a matter of law, be disregarded by the examiner. [*In re Merck*, 231 USPQ 375, 380 (Fed. Cir. 1986)]

Issue 5 - The applicability of the decision *In re Adamson*.

In the office action of June 7, 1993, the examiner indicated that no showing (even if applicants have made one),

would be persuasive in view of the decision *In re Adamson*. Although *In re Adamson* teaches that optical isomers *per se* are normally obvious over the corresponding known racemate, the decision should not be extended to stand for the proposition that a new method for using an isomer is unpatentable, particularly where, as here, the method unexpectedly provides an improved therapeutic ratio. For example, the claims of U.S. patent 4,851,444 (to Sunshine et al.) cover a method for using S-(+)-ibuprofen for onset-hastened analgesia, although (S)-ibuprofen *per se* was well known at the time of filing the application for a new use.

In *Adamson*, the CCPA held that in establishing that one isomer was more potent, the applicants had "done no more than what is suggested by the prior art and have ascertained no more than what would be expected by one skilled in the art" [Emphasis added]. Applicants' showing goes far beyond the evidence of enhanced potency at issue in *Adamson*. In the present case, applicants have shown that the resolution of the racemate and the use of R-(-)-albuterol substantially free of its S-isomer would provide therapy for asthma while simultaneously reducing side effects. As explained above, this is not suggested by the prior art. To the contrary, the art suggests that there would be no reduction in side effects. Thus, the decision in *Adamson* has no bearing on the patentability of this application.

Respectfully submitted,

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Sheet 1 of 1

DEC 36 1993 PAT. & TRADE MARK

INFORMATION DISCLOSURE CITATION

Docket No. 0701.027B	Serial No. 08/163,581
Applicant: Barberich et al.	
Filing Date:	Group: 1205

U.S. PATENT DOCUMENTS

Examiner Initial		Document Number	Date	Name	Class	Subclass	Filing Date If Appropriate

FOREIGN PATENT DOCUMENTS

		DOCUMENT NUMBER	Date	Country	Class	Subclass	Translation	
							Yes	No
KD	A	2255503	7/1992	Great Britain	—	—	X	

Other Documents (including Author, Title, Date, pertinent public etc.)

Examiner KD Date Considered 2/24/94

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THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Barberich et al.

Serial No.: 08/163,581 Group Art Unit: 1205

Filed: December 7, 1993 Examiner: unknown

Title: METHOD FOR TREATING ASTHMA USING OPTICALLY PURE R(-) ALBUTEROL

NOTIFICATION OF CHANGE IN CORRESPONDENCE ADDRESS

TO: HON. COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

Dear Sir:

Notification is hereby given that effective January 1, 1994 the correspondence address for the above-referenced application is:

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UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
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Washington, D.C. 20231

SERIAL NUMBER	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/163,581	12/07/93	BARBERICH	T SPC8905

EXAMINER
HENLEY, T.

12M2/0225

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ART UNIT	PAPER NUMBER
1205	36

DATE MAILED: 02/25/94

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☒ Responsive to communication filed on 12/7/93 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), _____ days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☐ Notice of References Cited by Examiner, PTO-892.
2. ☒ Notice re Patent Drawing, PTO-948.
3. ☒ Notice of Art Cited by Applicant, PTO-1449.
4. ☒ Notice of Informal Patent Application, Form PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☒ Claims 1-6, 8 and 15-18 are pending in the application.
   Of the above, claims _____ are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 1-6, 8 and 15-18 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice re Patent Drawing, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____ has (have) been ☐ approved by the examiner. ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed on _____ has been ☐ approved. ☐ disapproved (see explanation).
12. ☐ Acknowledgment is made of the claim for priority under U.S.C. 119. The certified copy has ☐ been received ☐ not been received
    ☐ been filed in parent application, serial no. _____; filed on _____
13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

PTOL-326 (Rev. 9-89)

CLAIMS 1-6, 8 AND 15-18 ARE PRESENTED FOR EXAMINATION

Applicants' amendment, preliminary remarks and the Information Disclosure Statement filed December 7, 1993 have been received and entered into the application. Accordingly, the specification at page 1 has been amended and as reflected by the attached, completed form PTO-1449, the submitted reference has been considered.

Claims 1-6 and 15-18 remain rejected under 35 U.S.C. § 103 as being unpatentable over Chemical Abstracts 89:123259m (Muttan et al.), already of record, for the reasons of record as maintained in the last Office action dated August 12, 1993.

Applicants' arguments have been carefully considered, but fail to persuade the Examiner of error.

Applicants have averred that the reference does not teach or suggest the use of an optically pure isomer of albuterol either alone or in combination. While the Examiner does agree that an optically pure isomer of albuterol is not highlighted, it cannot be agreed that such an isomer is not suggested by the authors. The individual isomers would have been obvious variants over the corresponding racemate because of their presence in the racemate. It would further have been expected that each isomer would not possess the same efficacy

or side effect profile since the racemate would be expected to exhibit the combined effects of the isomers.

Also, it is argued that the reference teaches to lower the side effects associated with albuterol and thus away from the presently claimed invention because of the adjunctive use of hydroxyzine. Applicants find support for this position in the statement by Muittari et al. that "a combination of salbutamol and hydroxyzine seems, therefore, to be one rational means of treating asthma with fewer side effects than the salbutamol-hydroxyzine-theophylline mixture, but still about the same effectiveness". The Examiner, however, cannot agree and finds this statement to mean that the salbutamol-hydroxyzine combination produced fewer side effects than the salbutamol-hydroxyzine-theophylline combination because in the former, theophylline, a known central nervous system stimulant, was absent.

Applicant further argues that it would have only been obvious to employ one of the isomers of the racemate if it were obvious that one of the isomers provided an advantage over the other. However, as expressed above, it would have been obvious to the skilled artisan that each isomer would not possess the same efficacy or side-effect profile as the other given that the activity exhibited by the racemate would have been recognized as being the result of the additive actions of each isomer.

Applicants also offer at page 5 that "it is worth noting that the mere fact that enantiomers exist does not render the use of a particular enantiomer obvious" (emphasis original). The Examiner cannot concur given the court's finding in In re Adamson et al., 275 F2d 952, 125 USPQ 233 (CCPA 1960) and Brenner et al. v. Ladd, Comr. Pats., 171 F2d 319, 80 USPQ 150 (CCPA 1948) that an optically active isomer is unpatentable over a prior art racemate or optical isomer of opposite rotation in the absence of unexpected or unobvious beneficial properties.

Thus, for these reasons, the claims are deemed to be properly rejected.

Claims 1-5 remain rejected under 35 U.S.C. § 103 as being unpatentable over Brittain et al., Hartley et al. and Buckner et al., each of record, for the reasons of record as maintained in the last Office action in further view of Hawkins et al, also already of record.

Applicants' arguments have been carefully considered, but fail to persuade the Examiner of error in his determination.

Respecting Brittain et al., applicants conclude at page 6 of their remarks that "from a study of the Brittain reference one may conclude nothing definitive regarding either the selectivity or R vs racemic or of the potency of R vs racemic." However, the statement in Brittain at the sentence bridging pages 146-7 that "It was not surprising therefore, to find that (-) salbutamol was much more active than (+) salbutamol." clearly speaks to the contrary.